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Interventions for improving outcomes in patients with multimorbidity in primary care and community settings.

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Interventions for improving outcomes in patients with multimorbidity in primary care and community settings (Review)

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TABLE OF CONTENTS

[Intervention Review]

Interventions for improving outcomes in patients with multimorbidity in primary care and community settings

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ABSTRACT

Background

Many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity. While this is not a new phenomenon, there is greater recognition of its impact and the importance of improving outcomes for individuals affected. Research in the area to date has focused mainly on descriptive epidemiology and impact assessment. There has been limited exploration of the effectiveness of interventions for multimorbidity.

Objectives

To determine the effectiveness of interventions designed to improve outcomes in patients with multimorbidity in primary care and community settings. Multimorbidity was defined as two or more chronic conditions in the same individual.

Search methods

We searched MEDLINE, EMBASE, CINAHL, CAB Health, AMED, HealthStar, The Cochrane Central Register of Controlled Trials (CENTRAL), the EPOC Register and the Database of Abstracts of Reviews of Effectiveness (DARE), and the EPOC Register in April 2011.

Selection criteria

We considered randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs), and interrupted time series analyses (ITS) reporting on interventions to improve outcomes for people with multimorbidity in primary care and community settings. The outcomes included any validated measure of physical or mental health, psychosocial status including quality of life outcomes, well-being, and measures of disability or functional status. We also included measures of patient and provider behaviour including measures of medication adherence, utilisation of health services, and acceptability of services and costs.

Data collection and analysis

Two review authors independently assessed studies for eligibility, extracted data, and assessed study quality. Meta-analysis of results was not possible so we carried out a narrative synthesis of the results from the included studies.

Main results

Ten studies examining a range of complex interventions for patients with multimorbidity were identified. All were RCTs and there was low risk of bias. Two of the nine studies focused on specific co-morbidities. The remaining studies focused on multimorbidity, generally in older patients. All studies involved complex interventions with multiple elements. In six of the ten studies, the predominant intervention element was a change to the organisation of care delivery, usually through case management or enhanced multidisciplinary team work. In the remaining four studies, the interventions were predominantly patient oriented. Overall the results were mixed with a trend towards improved prescribing and medication adherence. The results indicate that it is difficult to improve outcomes in this population but that interventions focusing on particular risk factors or functional difficulties in patients with co-morbid conditions or multimorbidity may be more effective. Cost data were limited with no economic analyses included, though the improvements in prescribing and risk factor management in some studies provided potentially significant cost savings.

Authors' conclusions

This review highlights the paucity of research into interventions to improve outcomes for multimorbidity with the focus to date being on co-morbid conditions or multimorbidity in older patients. The limited results suggest that interventions to date have had mixed effects but have shown a tendency to improve prescribing and medication adherence, particularly if interventions can be targeted at risk factors or specific functional difficulties in people with co-morbid conditions or multimorbidity. There is a need for clear definitions of participants, consideration of appropriate outcomes, and further pragmatic studies based in primary care settings.

PLAIN LANGUAGE SUMMARY

Improving outcomes for people with multiple chronic conditions

Many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity. This review aimed to identify and summarise the existing information about the effectiveness of any healthcare programmes or interventions to improve outcomes for people with multimorbidity in community settings. We identified ten studies, some of which focused on specific combinations of conditions, whereas others focused on multiple conditions in general, particularly in elderly patients. The majority of interventions involved changes to the organisation of care delivery though some studies had more patient focused interventions. There were mixed effects on physical health status but some improvements in prescribing and taking medication. Overall the results indicate that it is difficult to improve outcomes in this population, but that focusing on particular risk factors or functional difficulties in patients with co-morbid conditions or multimorbidity may be more effective. There is a need for further studies on this topic.

BACKGROUND

There has been increasing focus on the enormous personal and societal burden of ill-health caused by chronic disease. The World Health Organization has emphasized the importance of organising healthcare delivery systems to improve health outcomes and have stressed the importance of building integrated healthcare systems that can address chronic disease management (WHO 2002). This can be done by focusing on generic chronic care models, as has happened mainly in the USA, or by developing national systems focusing on single chronic conditions as has happened with the National Service Frameworks in the UK (Lewis 2004). However, many people with chronic disease have more than one chronic condition, which is referred to as multimorbidity (Fortin 2005). While this is not a new phenomenon, there is greater recognition of its impact and the importance of improving outcomes for individuals affected (Fortin 2007; Smith 2007).

How interventions might work

Given the complexity of managing patients with multiple chronic conditions, potential interventions are likely to be complex and multifaceted if they are to address the varied needs of these patients. We anticipated that a variety of intervention types could work to improve outcomes for patients with multimorbidity and could be included within the scope of this review. The EPOC Cochrane review group have developed a taxonomy that defines intervention types. We have used this taxonomy to define health service and patient oriented interventions that have been designed to improve outcomes of people or populations with more than one chronic

condition.

1. Professional interventions: For example, education designed to change the behaviour of clinicians.

Such interventions may work by altering professionals awareness of multimorbidity or providing training or education designed to equip clinicians with skills in managing these patients thus improving their healthcare delivery.

2. Financial interventions: For example, financial incentives to providers to reach treatment targets.

Such interventions might work by incentivising health service delivery and providing resources to extend consultation length for patients with multimorbidity.

3. Organisational interventions: These can be further divided into organisational changes delivered through practitioners or directly to patients. For example, any changes to care delivery such as case management or the addition of different healthcare workers such as a pharmacist to the healthcare team.

Such interventions may work by changing care delivery to match the needs of patients with multimorbidity across a range of areas such as coordination of care, medicines management, or use of other health professionals such as physiotherapists and occupational therapists to address needs relating to physical and social functioning.

4. Patient oriented interventions: This would include any intervention directed primarily at patients, for example, patient education or support for self-management.

Such interventions might work by improving self-management, thus enabling patients to manage their conditions more effectively and to seek appropriate health care.

5. Regulatory interventions: For example, changes to local or national regulations designed to alter care delivery in order to improve outcomes.

Such interventions might work by introducing regulatory changes that facilitate and enable the funding of care that is directed towards those with complex health needs. An example could be the introduction of free primary care for patients with multimorbidity on the basis that preventive care might prevent subsequent more costly hospital admissions. While we did not find these types of interventions, we believe they could exist and would fall within the scope of this review for future updates.

We anticipated that organisational type interventions might predominate. We were aware that there had been a focus on case management, based mainly in health maintenance organisations in the USA. There is a Cochrane review of case management being carried out (Zwarenstein 2000) which is investigating whether case management may improve health outcomes. In that review, case management is defined as the explicit allocation of co-ordination of tasks to an appointed individual or group and it is postulated that the function of co-ordination is so important and specialised that responsibility for carrying it out needs to be explicitly allocated. Our review included studies where case management was employed but only if it was specifically directed towards individuals identified as having multimorbidity.

The implementation of the Family Medicine Groups in the Province of Quebec, Canada, was another example of an organisational intervention as it involved new forms of shared responsibilities between physicians and nurses (Clair 2000). Another example in the UK was the community matrons programme, which is being delivered through primary care trusts and is based on nurse provided case management for patients with complex care needs including those with multimorbidity (London DOH 2005). It is similar to previous programmes delivered through social services in the 1990s and there have been concerns expressed at the feasibility of achieving the programme targets without real integration of primary and specialist services (Murphy 2004).

There have been no reviews of the effectiveness of such interventions for patients with multimorbidity.

Why it is important to do this review

Individuals with multimorbidity are more likely to die prematurely (Poses 1996), be admitted to hospital, (Librero 1999) and have longer hospital stays (Rochon 1996). They have poorer quality of life, loss of physical functioning (Bayliss 2004; Fortin 2004; Fortin 2006a), are more likely to suffer from depression, and to be receiving multiple medications consequently having difficulties with adherence (Townsend 2006). Prevalence studies of multimorbidity have been carried out in different countries indicating that, particularly in those over 60, the majority of patients attending family primary care services had more than one chronic condition (Fortin 2006b; Hoffman 1996; van den Akker 1998; Wolff 2002). A subgroup of these patients have a debilitating combination of conditions that have a high impact on their own lives but also on their utilisation of health services (Parmelee 1995; Smith 2008). These individuals, who could be referred to as having high impact multimorbidity, can be difficult to manage, resulting in frequent health care visits, frequent emergency hospital admissions, and repeated investigations with enormous cost for the individuals and for the healthcare system involved. A UK report has examined the costs associated with this group of patients who are described as 'high impact users' on the basis of their frequent emergency admissions (Foster 2006).

There is a clear recognition of the need for integrated care of multiple conditions (Stange 2005). The clinical care of these patients is complex. The evidence base for managing chronic conditions is based largely on trials of interventions for single conditions and individuals with multimorbidity are often excluded from such studies. (Fortin 2006b; Starfield 2001). Their clinical care may be fragmented with involvement of both primary care and multiple

specialists who may not be communicating effectively with each other. Starfield has found that patients with a high morbidity burden have a higher use of specialists even for conditions that are normally managed in primary care, and concludes that there is a need for a better understanding of the roles of generalists and specialists in managing these patients (Starfield 2005).

OBJECTIVES

To determine the effectiveness of health service or patient oriented interventions designed to improve outcomes in patients with multimorbidity in primary care and community settings. Multimorbidity was defined as two or more chronic conditions in the same individual.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled before and after studies (CBAs) meeting EPOC quality criteria, and interrupted time series analyses (ITS) (where there is a clearly defined point in time when the intervention occurred and at least three data points before and three data points after the intervention). Studies published in all languages were eligible for inclusion.

Types of participants

Participants included people or populations with multimorbidity receiving care in a primary or community care setting. We adopted the most widely used definition of multimorbidity, that is, the co-existence of multiple chronic diseases and medical conditions in the same individual, usually defined as two or more conditions (Fortin 2004; van den Akker 1998). We used the WHO definition of chronic disease, which is "health problems that require ongoing management over a period of years or decades" (WHO 2002).
We included all studies that identified participants or sub-groups of participants on the basis of multimorbidity, as defined by the study authors. We did not include studies or groups of patients within studies where multimorbidity was assumed to be the norm on the basis of patients' age as the interventions were not being targeted specifically at multimorbidity and its recognised complications. This included studies where interventions were directed at communities of people based on location or age of participants in which participants were presumed to have multimorbidity on the basis of their age or residence in a nursing home.

Types of interventions

We included any type of intervention that was specifically directed towards a group of patients defined as having multimorbidity. Only interventions based in primary care and community settings were included. Interventions included family doctors, nurses, or other primary care professionals. Primary health care was defined as providing "integrated, easy to access, health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practicing in the context of family and community" (Vaneslow 1995). However, not all countries have clearly defined primary care systems (Starfield 1998) so we included care delivered in community settings by individuals fulfilling the basic criteria for primary care, i.e. if they are available to treat all common conditions in all age groups and have an ongoing relationship with their patients. While some specialists may deliver components of primary care to their patients, practitioners were not included unless they fulfilled the definition of being available to treat all conditions and have an ongoing relationship with their patients.
Interventions were classified as 'simple' if they used one identifiable component or multifaceted if they incorporated more than one feature.
We categorised interventions using the EPOC taxonomy presented in the Background section. Where interventions had multiple elements, we defined each element within the taxonomy and highlighted the predominant element of the intervention. See Table 1.
The following interventions were excluded:

- Professional educational interventions or research initiatives where there was no specified structured clinical care delivered to an identified group of patients with multimorbidity.

- Interventions targeted at one condition only. This commonly occurs where people with an identified chronic condition are screened for co-morbid depression and are then treated for depression.
- Interventions targeted at co-morbid conditions where the intervention was targeted solely at one condition. This commonly arises in relation to chronic disease and co-morbid depression, so called 'depression plus one studies'. These are increasingly common as the link between depression and most chronic conditions has now been well established. We therefore excluded such studies if the intervention was only targeted at the depression and did not take into account the full extent of the multimorbidity.

Types of outcome measures

Studies were included if they reported any objective, validated measure of:

- Patient physical or mental health outcomes.

- Patient psychosocial outcomes including quality of life outcomes, well-being, and measures of disability or functional status.
- Utilisation of health services including hospital admissions.
- Patient behaviour including measures of medication adherence, and other objective measures such as goal attainment (Cox 2002; Gordon 1999; Kiresuk 1968). Self-report behaviour outcomes were included if they were measured with a validated scale.
- Provider behaviour.
- Acceptability of the service to patients and providers, if this was reported in a study that reported patient outcomes or provider behaviour.
- Economic outcomes including full economic analyses incorporating measures of efficiency or effectiveness in relation to costs or direct costs depending on what was reported in included studies.

Attitude and knowledge outcomes were excluded during the preparation of the protocol as we wanted to include objective measures of professional behaviour or patient outcomes. Treatment satisfaction was included if it was reported in a study that also reported other objective outcome measures.

Search methods for identification of studies

Electronic searches

The search strategy was particularly challenging given the lack of a mesh term for multimorbidity. In addition, we were aware from existing epidemiological literature that the recognition of multimorbidity as a concept is relatively recent. Multimorbidity is sometimes used synonymously with the term comorbidity, though this tends to be used in relation to diseases that coexist with an index disease under study (de Groot 2004). However, comorbidity is a MeSH term, whereas multimorbidity is not, so we included both terms in our search. For pragmatic reasons we limited the MEDLINE search to articles indexed from 1990 onwards.The following electronic databases were searched in April 2011:

Database Name	Interface
AMED --Allied & Complimentary Medicine (1985- current)	Ovid
CAB Abstracts (1973-current)	Ebsco
CINAHL-Cumulataive Index to Nursing & Allied Health Literature (1981-current)	Ebsco
Cochrane Library (CENTRAL)	Wiley
EMBASE (1980-current)	Ovid SP
EPOC Register (from The Effective Practice & Organization of Care Group, Cochrane Collaboration)	Reference Manager
HealthStar (1999 - current)	Ovid SP
MEDLINE (1990-current)	Ovid SP
MEDLINE In-Process & Other Non-Indexed Citations	Ovid SP
MEDLINE Daily Update	Ovid SP
DARE	Wiley

The search strategy published in the protocol was not used and the search strategy recorded for the 2007 search of MEDLINE was revised in 2009 to better capture the concept of multimorbidity. Results of the search were limited by filters for study design and an extensive list of intervention terms. Search strategies are provided in appendices as follows: MEDLINE Appendix 1; EMBASE Appendix 2; CAB Abstracts Appendix 3; Cochrane Central Register or Controlled Trials Appendix 4; CINAHL Appendix 5. The MEDLINE strategy was used in Healthstar and AMED; the Cochrane search strategy was used in DARE.

Searching other resources

(a) Reference lists of all included papers were searched.
(b) Authors of relevant papers were contacted regarding any further published or unpublished work.
(c) We had planned to contact authors of other reviews in the field of multimorbidity that were retrieved during the search process regarding relevant studies that they may be aware of, but no other reviews were identified.

Data collection and analysis

Obtaining studies and determining eligibility for the review

Potentially relevant studies were determined by review of the abstracts of search results. Full text copies of all articles identified as potentially relevant were retrieved. Two review authors (SS and HS) independently assessed each retrieved article for inclusion.

Data abstraction

Two review authors (SS and HS) undertook data abstraction and cross checked data abstraction forms using a modified version of the EPOC data collection checklist. Disagreements about eligibility and quality were resolved by consensus between the review authors. Where questions remained, we planned that the abstract would be reviewed by a third review author or, if necessary, by referral to the Cochrane contact editor. We referred one study (Zhang 2008) to EPOC regarding its design and this was excluded.

Quality

The risk of bias in all included studies was assessed by two independent review authors using standard EPOC criteria (see ADDITIONAL INFORMATION, ASSESSMENT OF METHODOLOGICAL QUALITY under GROUP DETAILS).
The following data were extracted for all included studies:
(1) Details of the intervention: a full description of the intervention was extracted as were details regarding aims; clinical protocols; use of case workers; remuneration/ payment systems; providers involved; and theoretical framework on which the intervention was based.

(2) Participants:
- Patients: nature of multimorbidity and how determined
- Providers: specialist and primary care providers involved; family members

(3) Clinical setting.
(4) Study design.
(5) Results. Results were organised into:
- Health outcomes
- Psychosocial outcomes including quality of life outcomes
- Process of care including health service utilisation and changes in patient and provider behaviours
- Patient and provider acceptability
- Economic outcomes. We reported the economic outcomes of eligible studies. Where economic analyses were available linking costs to effectiveness or efficiency, we planned to provide details on the measures used by authors. Where direct costs were reported alone, we indicated whether these costs related to society, the health service, or the patients. We also reported, where possible, costs in relation to the specific year and currency presented; whether costs related to total costs or simple fees charged; what was included in the cost calculations; and over what time period costs were calculated.

Reporting

We reported data in natural units for each study.
For RCTs, we reported results in terms of:
(1) Absolute difference (mean or proportion of outcome in intervention group minus control at study completion).
(2) Relative percentage difference (absolute difference divided by post-intervention score in the control group).
Standardised effect sizes are presented in tables where possible, i.e. where studies reported relevant data for their calculation.
For ITS we had planned to report two effect sizes:
(1) The change in the outcome immediately after the introduction of the intervention.
(2) The change in the slope of the regression lines.
However, no ITS studies were identified.

If data were missing, authors were contacted to obtain the information.

Data analysis

Analysis of primary outcomes

Included studies measured similar outcomes using different methods. These included either continuous variables (such as blood pressure) or dichotomous process measures (such as proportion of patients with diabetes receiving a structured annual review for complications).

Standardised effect sizes for continuous measures were calculated by dividing the difference in mean scores between the intervention and comparison group in each study by an estimate of the pooled standard deviation.

We planned to carry out meta-analysis if studies were identified that were similar in terms of settings, patients, interventions, outcome assessment and study methods. However, this was not possible so we carried out a narrative synthesis of the results from the included studies.

Methods for reanalysis of RCTs, CCTs and CBAs with potential unit of analysis errors

We planned to re-analyse studies with unit of analysis errors, where indicated and where possible. None of the included studies had unit of analysis errors.

Methods for reanalysis of ITS comparisons with inappropriate analysis

We planned to use time series regression to re-analyse each comparison, where indicated and where possible. Additional analyses of ITS would have been based on EPOC criteria. No ITS studies were identified

Additional analyses

Subgroup analyses

We had planned, if possible, to consider subgroup analyses based on the degree of multimorbidity of participants. This would have been based on the number of conditions per person. This was not possible.

Exploring heterogeneity

We planned to prepare tables and funnel plots comparing effect sizes of studies grouped according to potential effect modifiers (for example, simple versus multifaceted interventions) if sufficient studies had been identified.

If there had been enough studies, we had planned to use meta-regression to see whether the effect sizes could be predicted by study characteristics. These could, for example, include duration of the intervention, age groups, and simple versus multifaceted interventions (Cooper 1994). We also considered formal tests of homogeneity (Petitti 1994). None of these quantitative methods were possible for this version of the review but will be considered for future review updates.

Ongoing studies

Ongoing studies were identified and described where possible together with an estimate on reporting date if available.

RESULTS

Description of studies

Search results

The search was carried out in January 2007, and repeated in October 2008, February 2009 and April 2011. The following number of articles were identified in each database (following removal of duplicates):

MEDLINE: 15984

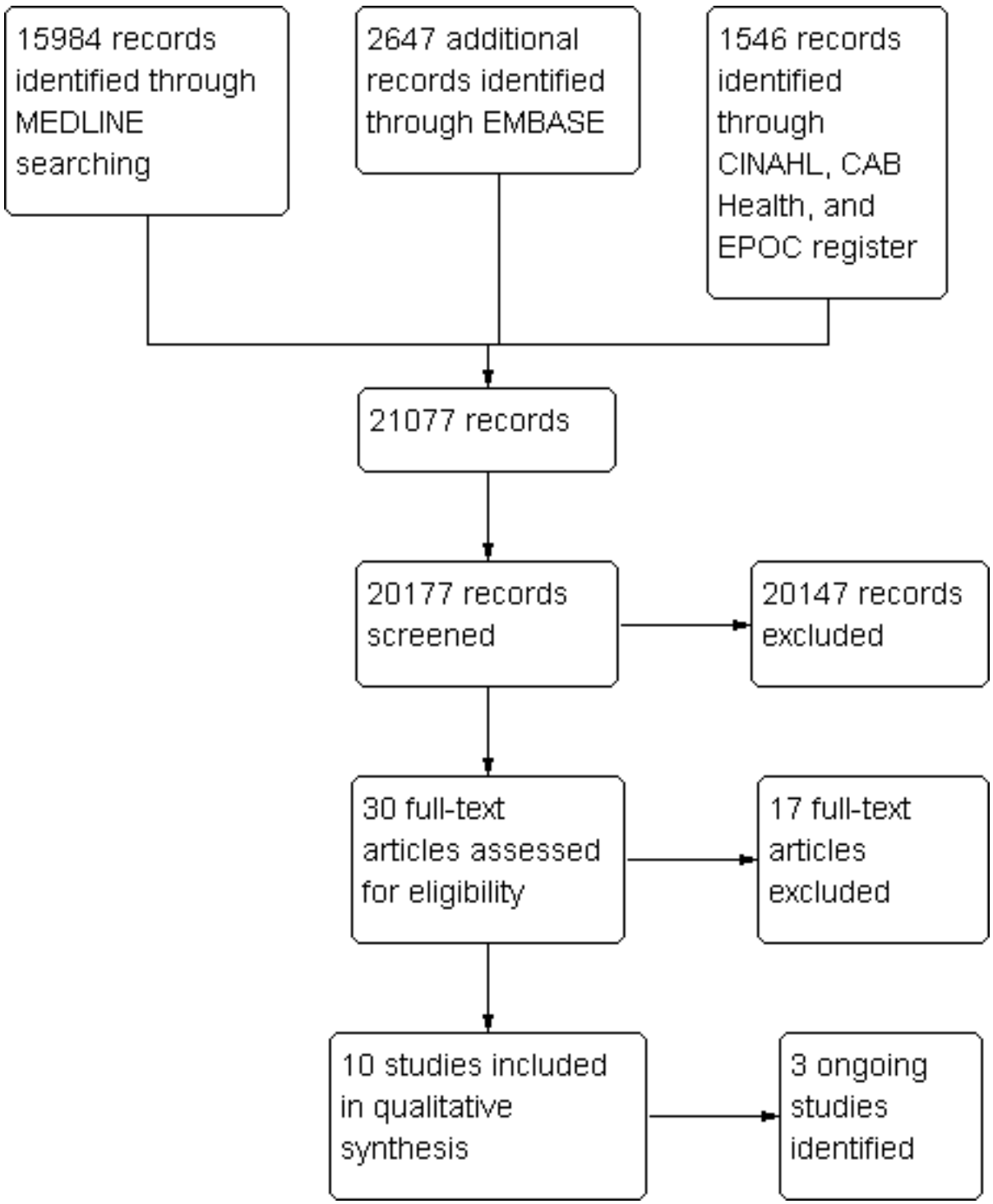
EMBASE: 2647

CINAHL, CAB Health and EPOC: 1546

Total: 20177

The search process is outlined in Figure 1. Thirty full papers were screened for eligibility by two reviewers (SS and HS) and we sought advice on the eligibility of one paper from the EPOC editorial base. Details of the 17 excluded papers are provided in the Table: Characteristics of excluded studies.

Figure 1. Study flow diagram.



We identified three ongoing studies which are described in the Table: Characteristics of ongoing studies.

Overview of included studies

We identified ten studies eligible for inclusion in the review (see Table: Characteristics of included studies). All ten were randomised controlled trials (RCTs). There were a total of 3357 patients included. The studies varied in duration from eight weeks to two years, with the majority lasting 6-12 months.

Eight of the ten studies included patients with a broad range of conditions (Boult 2011, Eakin 2007, Gitlin 2006, Hocchalter 2010, Hogg 2009, Krska 2001, Lorig 1999 and Sommers 2000), whereas the remaining two focused more on comorbidities: coexisting depression and hypertension (Bogner 2008); coexisting depression and diabetes and/ or heart disease (Katon 2010). All were set in primary care or community settings in the USA, apart from Krska 2001 which was set in the UK National Health Service and Hogg 2009 which was set in Canada. Five were funded by a government or university grant (Gitlin 2006, Hogg 2009, Katon 2010, Krska 2001, Lorig 1999) and the remaining studies were funded by charitable foundations. None were funded directly by the pharmaceutical industry.

In the majority of included studies, the comparator was usual medical care which was supplemented by a newsletter or leaflet in Eakin 2007 and Gitlin 2006 or assessment but no follow-on intervention in Bogner 2008, Katon 2010 and Krska 2001. Hocchalter 2010 was the only study that used an attention control, with control patients also attending a group session, but one which was based on an unrelated topic. No study specifically reported consumer involvement in the intervention design.

Description of interventions

The interventions were all multifaceted and brief descriptions for each study are provided in the Characteristics of included studies table.

As outlined in the methods, we used the EPOC taxonomy of interventions to describe and categorise the interventions tested in these studies. While the interventions identified all involved multiple components they could be divided into two main groups: Predominantly organisational interventions (Bogner 2008, Boult 2011, Hogg 2009, Katon 2010, Krska 2001, Sommers 2000) or predominantly patient oriented (Eakin 2007, Gitlin 2006, Hocchalter 2010, Lorig 1999). No study involving financial or regulatory type interventions were identified. We have included an additional table which outlines intervention elements and indicates which elements featured in each of the included studies (Table 1).

Risk of bias in included studies

The risk of bias for individual studies is reported in the Characteristics of included studies table. Overall the studies were of reasonable quality with low risk of bias though consideration of contamination of control patients was generally inadequate.

Allocation concealment was done in six of the ten studies (Boult 2011, Gitlin 2006; Hogg 2009, Katon 2010, Krska 2001, Sommers 2000) but was unclear in the remainder. Baseline measurement of outcomes was carried out in all studies. All reported adequate follow-up of participants except Lorig 1999 who did not provide specific details for the multimorbidity subgroup, though follow up for the overall study was adequate. Objective outcomes were used in all studies except Krska 2001 and Hogg 2009, where this was unclear. Krska 2001 used a measure detailing pharmaceutical care issues (PCIs) which was a previously developed classification system modified for the study. Hogg 2009 collected data on chronic and preventive care delivery from patient records but there was no reporting of assessment of this process. Blinding of outcome assessment was done in six studies (Boult 2011, Gitlin 2006, Hocchalter 2010, Katon 2010, Lorig 1999, Sommers 2000). It was unclear in three studies (Bogner 2008, Eakin 2007, Hogg 2009) and not done in Krska 2001.

Only two of the ten studies had a cluster design ensuring no contamination of control patients (Boult 2011, Sommers 2000). Contamination of control patients was unlikely in a further four studies where the intervention was directed at patients rather than providers (Eakin 2007, Gitlin 2006, Lorig 1999 and Hocchalter 2010) but was possible in the remaining studies (Bogner 2008, Hogg 2009, Katon 2010, Sommers 2000). However, Katon 2010 et al provided an additional appendix outlining consideration of potential contamination and indicated it was minimal and if it had occurred, would have diluted rather than increased the significant effect size of their intervention.

The two cluster randomised controlled trials (Boult 2011; Sommers 2000) had accounted for clustering effects in their analysis so there were no unit of analysis errors.

Effects of interventions

Effects by type of interventions

As outlined above the interventions were either organisational or patient oriented. It must be stressed that as all interventions were complex and multi-faceted, there are overlapping elements across these two divisions. We have summarised the results by intervention type in Table 2.

The results indicate that organisational type interventions that are targeted at specific risk factor management or focused areas where patients have difficulties, such as with functional ability or medicines management, are more likely to be effective. Organisational interventions that have a broader focus such as case management or changes in care delivery seem less effective. Patient oriented interventions that are not linked to healthcare delivery seem less effective although there was one exception, Gitlin 2006, which found significantly reduced mortality following a focused

intervention targeting functional difficulty and fall prevention (Int (n= 160): (0.056) Con (n= 159): (0.132), Absol diff 7.6%, Rel% diff 58%).

Organisational interventions

Six studies had organisational type interventions (Bogner 2008; Boult 2011; Hogg 2009; Katon 2010; Krska 2001; Sommers 2000). These predominantly involved case management and co-ordination of care or the enhancement of skill mix in multidisciplinary teams.

1. Physical health outcomes

Bogner 2008 and Katon 2010 reported statistically significant improvements in blood pressure, though this was of minimal clinical significance in Katon 2010. Katon 2010 also reported statistically significant improvements in HBa1c and LDL cholesterol. The composite primary outcome in Katon 2010 included these three physical health outcomes combined with the depression score and was also significantly improved by the intervention. Hogg 2009 also reported HBA1c and blood pressure for patients who had diabetes (62 of 241) and/or hypertension (167 of 241) and found no significant difference following their intervention. Sommers 2000 reported symptom scores relating to physical health and found no differences in symptom scores (see Table 3).

2. Mental health outcomes

Three studies presented data on mental health outcomes (Bogner 2008, Katon 2010, Sommers 2000). Two showed significant improvements in outcomes, all of which related to depression (Bogner 2008, Katon 2010), whereas Sommers 2000 reported no difference in depression scores (see Table 4).

3. Psychosocial outcomes

Four studies reported psychosocial outcomes (Hogg 2009, Katon 2010, Krska 2001, Sommers 2000). Krska 2001 stated that SF36 scores had been analysed across eight domains at study completion and showed no difference between groups, but did not present actual data. Katon 2010 found significant improvements in HEQol scores following their intervention. Sommers 2000 found no significant differences in SF36 scores or HAQ scores, but did find significant improvements in social activities counts in the intervention group (see Table 5).

4. Utilisation of health services

Five studies reported outcomes on health services utilisation (Boult 2011, Hogg 2009, Katon 2010, Krska 2001, Sommers 2000). Sommers 2000 reported significant improvements for intervention group patients across a variety of measures relating to hospital admissions, whereas Boult 2011, Hogg 2009, Katon 2010 and Krska 2001 found no significant difference in admission related outcomes, though numbers of admissions in most of these studies were very small.

Three studies reported data in relation to health service visits with a range of providers (Boult 2011, Hogg 2009, Sommers 2000) none of which showed predominantly significant improvements in health service use (see Table 6).

5. Patient behaviour

5.1 Medication use and adherence

Only one study reported measures relating to medication use and adherence. Bogner 2008 found significant improvements in proportions of intervention patients adhering to both antidepressant and antihypertensive medication as measured using automated counting systems in the caps of medicine bottles (MEMS caps) (see Table 7).

5.2 Health related behaviours

Two studies provided data on a variety of outcomes relating to health behaviours by patients (Katon 2010, Sommers 2000). Katon 2010 found no difference in relation to adherence to diet and exercise. Sommers 2000 found no significant changes in a nutrition checklist score (see Table 8).

5. Provider behaviour

Prescribing

Two studies reported measures relating to practitioner prescribing or medicines management, both of which indicated significant benefits for intervention patients. Katon 2010 reported a measure examining one or more medication adjustments for five classes of drugs related to the co-morbid conditions being studied and found statistically significant differences for four of these five groups. Krska 2001 reported a significant reduction in pharmaceutical care issues in intervention patients which would have been mediated by changes in both pharmacist intervention and GP prescribing.

Other provider behaviours

Provider behaviours relating to chronic disease management or preventive care were reported in two studies. Boult 2011 presented a validated measure called the Patient Assessment of Chronic Illness Care (PACIC) score, which is a patient assessment of the quality of care received. This score includes five elements and the aggregate quality score derived was significantly improved in the Guided Care intervention group. Hogg 2009 reported measures relating to chronic disease management and preventive care based on chart data and both were significantly improved in the intervention group (see Table 9).

6. Acceptability of services

Only two studies reported treatment satisfaction. Katon 2010 reported the proportion of patients moderately to very satisfied with treatment for depression and diabetes and heart disease at study completion. Significantly more intervention patients were satisfied with their care at study completion compared to those experiencing usual care. This was 86% for diabetes or heart disease care and 90% for depression care for intervention patients, compared with 70% and 55% respectively for control patients.

Boult 2011 also reported on the changes in satisfaction for providers as part of an overall examination of the effect of the intervention on providers. (Boult 2008) The measure incorporated changes in 11 domains of satisfaction with service provision; five domains relating to time spent with patients; six domains relating to provider knowledge of the patient, and four domains relating to care coordination. The only significant changes reported in the study were improvements in 5 of the 11 domains relating to sat-

isfaction with service provision.

7. Costs

Four studies provided data on costs (Boult 2011, Katon 2010, Krska 2001, Sommers 2000).

Leff 2009 et al provided initial cost data from Boult 2011 and indicated a saving related to Guided Care of $75,000 per guided care nurse [95% CI -$244,000 to $150,900] or $1364 per patient. However, these initial results were based on non-significant changes in outcomes and thus have wide confidence intervals. In addition, the final study results were subsequently published and indicated no significant intervention effect.

Katon 2010 reported the direct mean medical costs relating to the TeamCare intervention over a 12 month period as $1224 per patient. This study reported on an effective intervention and a full economic analysis is awaited.

Krska 2001 reported the mean medicine cost for the intervention and control groups at study completion and found a marginal benefit for the intervention, but this was not statistically significant.

Sommers 2000 reported a net saving per intervention patient of $90 though this did not include additional savings from fewer physician visits. It also excluded the costs of implementing the intervention, stated to be $118,950, mainly relating to salary costs (see Table 10).

Patient oriented intervention

Four studies had predominantly patient oriented interventions, as defined in the background section (Eakin 2007; Gitlin 2006; Hocchalter 2010, Lorig 1999). All four aimed to address patient health related behaviour and did not engage or intervene with health care providers directly. The results from these four studies were mixed and do not suggest that all patient oriented interventions are generally effective. However, the striking findings relating to mortality from one study were noteworthy, though must be interpreted with caution, as this was the only study in this review with such a finding (Gitlin 2006).

1. Physical health outcomes

Eakin 2007 included a sub-group of 175 urban Latino patients with at least two chronic conditions, and a health educator delivered a 16 week diet and physical activity intervention. This involved two face to face visits, three follow up phone calls, and three newsletters. At six month follow up, there were mixed results across three outcomes reported with significant improvements in dietary behaviour and support for healthy lifestyle, but no improvement in physical activity.

Gitlin 2006 produced a follow up paper looking at long tem effects of their intervention on mortality and found significantly reduced mortality in intervention patients, which persisted up to three and half years post intervention (Gitlin 2009).

2. Mental health outcomes

One study presented data on mental health outcomes (Lorig 1999) and found no difference in cognitive symptom management between groups at study completion (see Table 4).

3. Psychosocial outcomes

Four studies reported psychosocial outcomes (Eakin 2007, Gitlin 2006, Hocchalter 2010, Lorig 1999). Hocchalter 2010, Eakin 2007, and Lorig 1999 found no significant differences in a range of psychosocial measures. Gitlin 2006 reported six psychosocial measures by presenting difference in adjusted means between intervention and control groups at follow up and only two showed significant improvement (self-efficacy in relation to fear of falling and improvements in control oriented strategies). ADLs, IADLs, overall functional self-efficacy, and presence of home hazards were not significantly different (see Table 5).

4. Utilisation of health services

One study reported outcomes on health services utilisation (Lorig 1999) and reported significant improvements for intervention group patients across a variety of measures relating to hospital admissions. Lorig 1999 also reported on doctor and Emergency Department but found no significant improvements (see Table 6).

5. Patient behaviour

5.1 Medication use and adherence

No study with a patient oriented intervention reported on medication use and adherence.

5.2 Health related behaviours

Two studies provided data on a variety of outcomes relating to health behaviours by patients (Eakin 2007, Lorig 1999). Eakin 2007 reported significant improvements in diet behaviour scores and in changes in minutes of walking per week. Lorig 1999 found no significant differences in exercise measures or communication with doctors (see Table 8).

5. Provider behaviour

Prescribing and other provider behaviours

No study with a patient oriented intervention reported on provider behaviour.

6. Acceptability of services

No study with a patient oriented intervention reported on acceptability of services.

7. Costs

Two studies provided data on costs (Gitlin 2006, Lorig 1999).

Gitlin 2006 reported the direct costs associated with the intervention at $1222 per experimental participant. This incorporated $439 equipment costs and $783 therapy costs.

Lorig 1999 reported the mean direct cost of running the course for participants who completed it, though costs did not include the cost of accomodation as this was donated to the study. The significant reduction in hospital admissions shown by the intervention translated to a saving in healthcare costs per participant of $750 which the authors point out is ten times the cost of the intervention. This calculation was based on a presumed cost of $1000 per day if admitted to hospital (see Table 10).

Comorbidity vs multimorbidity studies

Two of the ten included studies focused on comorbidity rather than multimorbidity in general (Bogner 2008, Katon 2010). Table 2 presents the results across the range of outcomes and compares effects between these co-morbidity studies and the general multi-

morbidity studies. The co-morbidity studies showed more significant effects and were able to use more disease focused interventions and outcome measures.

DISCUSSION

Summary of main results

We identified ten studies eligible for inclusion in the review, all of which were randomised controlled trials with a generally low risk of bias. Even within this small number of studies, there was significant variation in participants and interventions. In two studies, the focus was on co-morbid conditions, meaning interventions could be directed at these pre-specified conditions. In the other studies, which included patients with multimorbidity, the focus tended to be on older patients and the interventions had multiple components incorporating different elements, making comparison between studies and between intervention elements difficult. We categorised the intervention components using the EPOC taxonomy and identified the predominant intervention element for each study. When examining the effectiveness of interventions by intervention type, we concluded that organisational type interventions that are targeted at specific risk factor management or focused areas where patients have difficulties, such as with functional ability or medicines management, are more likely to be effective. Organisational interventions that have a broader focus, such as case management or changes in care delivery, seem less effective. Patient oriented interventions that are not linked to healthcare delivery also seem less effective apart from one study (Gitlin 2006) which found significantly reduced mortality following a focused intervention targeting functional difficulty and fall prevention.

We have also presented results by outcomes pre-specified in the protocol. In general these results were mixed and inconclusive, particularly those relating to physical health outcomes. In fact, there was not a strong focus on physical health measures and this may reflect the challenge in research in multimorbidity when disease specific measures cannot be used, unless there is more of a comorbidity focus as in the hypertension/depression or diabetes/CHD/depression studies in this review.

There was limited effect on psychosocial outcomes and on outcomes relating to health service utilisation with mixed effects on hospital admission rates. Outcomes relating to prescribing, medication use, and adherence were measured in three studies and all found significant benefits. However, the studies may be too short for these benefits to translate into improvements in physical health outcomes. Five studies reported patient health behaviours outcomes and only one showed benefit.

Costs were presented in five studies but data was provided on direct costs only. The results relating to improved prescribing and risk factor management, particularly in the co-morbidity trials, indicate a potential for these interventions to reduce health service costs over longer periods of time.

Overall completeness and applicability of evidence

Most of the studies in this review are relatively recent reflecting the fact that this is a new area conceptually and that research to date has focused on description and impact rather than interventions. Earlier studies tended to focus on co-morbidity rather than multimorbidity in general. Two of the studies in this review had interventions that focused on co-morbid conditions and the significant improvements in outcomes is likely related to the strong focus in these interventions on targeting the specific conditions involved. It is more challenging to design interventions for people with a broad range of conditions. The studies that seem more effective in this group are those which had interventions targeted at specific areas of concern for patients with multimorbidity, such as medicines management and functional ability. One of the more recent studies involved a large well-designed and executed RCT of a broad organisational type intervention targeted at high risk individuals with multimorbidity, which found no significant benefit overall (Boult 2011). However, a pre-planned sub-group analysis indicated significant improvements in the use of some health services in the patients enrolled in one of the participating care plans (Kaiser-Permanente, n= 365, 43% of full sample). Boult 2011 postulated that this may have related to the fact that care was already more organised and structured in this system, so that Guided Care may simply have extended the existing approaches used in that setting wheras its implementation was more challenging in less organised systems. However, the results of sub-group analysis, even when pre-planned need to be interpreted with caution given the relatively small samples sizes involved. Nonetheless, the differences in these sub-groups highlight the importance of the healthcare delivery setting into which new interventions are added. Indeed, some of the patient oriented interventions seemed to run independently of patients' healthcare delivery, and most of these studies had limited effectiveness, highlighting the importance of considering the overall patient experience and integrating interventions into the healthcare system. The results of the patient oriented intervention studies are consistent with the Foster 2007 Cochrane review on lay led self-management support programme which concluded that there is no evidence that these interventions improve psychological health, symptoms or health-related quality of life, or that they significantly alter healthcare use.

The evidence from this review partially addresses the review question, i.e, what interventions can effectively improve outcomes in patients with multimorbidity. Interventions need to be targeted at populations with defined combinations of common conditions such as diabetes and depression or arthritis and heart disease or need to focus on targeted problems in multimorbidity populations, for example, management of multiple medications. How-

ever, even when interventions are targeted they may not be effective. The Haynes 2008 Cochrane review of Interventions for enhancing medication adherence concludes that "current methods of improving adherence for chronic health problems are mostly complex and not very effective" and suggests further research is needed. Patients with multimorbidity may have more specific problems with medicines use that relate to polypharmacy and managing complex drug treatment regimens, so medicines management interventions targeting these specific difficulties may be more effective.

As research in this area is increasing and a number of ongoing studies have been identified, we anticipate that the next update of the review will provide better evidence to inform policy makers and those planning services for individuals with multimorbidity.

Quality of the evidence

All of the included studies were randomised controlled trials. Overall they were of reasonable quality with minimal risk of bias, although consideration of contamination of control patients was occasionally inadequate. Multimorbidity is a complex area because participants can vary depending on definitions used. This limits the potential to reasonably combine study results for meta-analysis, and potentially limits the internal validity of the results of the review.

Potential biases in the review process

The review was carried out in accordance with EPOC guidelines and using the updated Cochrane Handbook. Potential limitations in the search process relate to the lack of a MeSH term for multimorbidity. This meant that we had to use broad search terms which led to a high yield of citations to be searched. However, the authors are active researchers in the field of multimorbidity and are unaware of any potentially eligible studies that were missed by the search. We were also unable to retrieve some missing data from authors. However, as no meta-analysis was undertaken this did not lead to any appreciable measurement bias.

Agreements and disagreements with other studies or reviews

We were unable to group sufficient numbers of studies with similar interventions in order to comment on which elements of interventions (e.g. the use of community pharmacists) seemed most effective and compare our review to other reviews of these interventions. The most consistent intervention element across all included studies was the use of case managers, but even these varied in that some were clinical case managers and others were administrative managers. The Cochrane review of the effect of case management on health care outcomes is ongoing but does plan to address differences in effectiveness between different types of case management.

AUTHORS' CONCLUSIONS

Implications for practice

Multimorbidity is common in clinical practice and there is limited evidence supporting specific interventions. The focus of an intervention will be different for a patient under or over 65, and the outcomes chosen should reflect this. Most of the multimorbidity studies in this review focused on older patients; however, it is important to address the needs of younger patients also as there are issues relating to employability and absenteeism. Acting upstream for younger patients with multimorbidity is preventive and has potential to bring about significant quality of life benefits for individuals as well as cost savings for healthcare systems. However, even in ageing populations, multimorbidity worsens outcomes so there is still likely to be room for improvement, at least in ambulatory care patients. This review suggests that targeting specific problems experienced by patients with multimorbidity may be more effective. We also need to recognize the importance of socioeconomic status and the impact of deprivation. Recent work in Scotland has highlighted that individuals in the poorest socioeconomic groups are more likely to develop multimorbidity at a younger age and more likely to die prematurely as a result (Barnet 2011).

The sub-group analysis from the Guided Care study suggests that multimorbidity interventions need to be integrated into existing healthcare systems for reasons of sustainability (Boult 2011). Independent interventions that do not integrate with existing healthcare systems will have difficulty with sustainability. Many of the included studies focused on integration of care between practitioners, but we also need to consider how we integrate interventions into healthcare systems.

The literature on multimorbidity indicates that it is generally associated with poorer outcomes for patients. However, it may be worth prioritising which outcomes should be addressed in an intervention. This should be addressed in the early stages of the development of a potential new intervention and we should focus on eliciting patients' values and preferences. Patients with multimorbidity are not only at higher risk of many adverse outcomes, but they also have competing outcomes. The more complex the case, the more we should think in terms of outcomes that are relevant across diseases, e.g, nutrition, living situations, function, symptom burden, survival, and active life expectancy. Having the patient participate in priority setting based on his/her values and preferences becomes both the rational and the ethical thing to do.

Within this review, interprofessional collaboration was embedded in all interventions. This is worth building on for future intervention development. Most of the included studies focused on changing professional care provision; it may also be worthwhile incorporating the patient perspective. This could be achieved by adopting a participatory approach to intervention development. Patients with multimorbidity, their family members, and a range of

professionals involved should be consulted during the modelling and exploratory phases of service and intervention planning.

Implications for research

Definitions

There is a need for a clear conceptual definition of multimorbidity and its differentiation from other related concepts such as co-morbidity, complexity, frailty, and vulnerability. We need specific measures to accurately classify patients. This will be particularly important given the need to account for the heterogeneity of multimorbidity; interventions could have differential effects depending on the definition or degree of multimorbidity and the socioeconomic status of participants.

Without these definitions and consideration of related concepts, the generalisability or applicability of studies for patients with multimorbidity (with a broader definition than only two or three fixed diseases) will be uncertain, as is the case for many of the studies in this review, particularly those with the specific co-morbidity focus.

We would also advocate for including multimorbidity as a MeSH term as the search strategy for this review and for ongoing work on multimorbidity is particularly complex and time consuming, given the growing concern and interest in the issue.

Study design

While the risk of bias was generally low in this review and all studies were RCTs, we acknowledge the difficulty of conducting optimal RCTs due to the heterogeneity of multimorbidity. So pragmatic trials or sequential RCTs may also be appropriate while still maintaining rigour.

Future studies need to carefully consider the comparison or control group, particularly in relation to contamination of control patients. Cluster randomised designs are likely to be optimal if interventions are delivered through care providers. This needs to be taken into account both in terms of power calculations and in the analysis of results.

Interventions

This review indicates that interventions that are targeted at either specific combinations of common conditions, or at specific problems for patients with multiple conditions, may be more effective. When designing interventions researchers should be clear about the theoretical assumptions underlying the intervention, consider its individual components and the evidence base behind each and then link these to outcomes as outlined below. They should also consider interventions that are likely to be reproducible and applicable within the context of primary care. The Medical Research Council Framework for the Design and Evaluation of complex interventions designed to improve health, provides useful guidance in designing and undertaking these trials. (MRC Framework 2008)

The majority of the evidence for effective chronic disease management has been based on a single disease paradigm. However, it is likely that participants in these trials had some degree of multimorbidity, though sicker patients may have been excluded. We should therefore seek to build on and apply the evidence regarding effective interventions for single conditions to patients with multimorbidity, rather than designing interventions with no consideration of the existing evidence base for single conditions.

In its broadest sense, multimorbidity encompasses a large variety of patients which must be considered as it is not pragmatic to design interventions that change systems completely. For this reason, parallel economic analyses that link outcomes to costs and benefits are better than providing simple cost data alone, which make comparison across studies difficult.

Outcomes

The challenge with multimorbidity is to define a set of outcomes that can be used for different combination of diseases, so there is a need for generic outcomes measures that incorporate physical functioning and quality of life that are responsive to change over time. Other outcomes to consider include goal attainment, self-care, self efficacy, health related quality of life, distress, adherence to treatment, behavioural changes regarding health habits, patient's knowledge about care plans, shared decision making, and participation in care. However, unless validated measures are used, many of these outcomes will not be comparable across studies. The recent work of PROMIS (PROMIS 2011) provides validated and useful patient reported outcomes that will be particularly relevant for those researching interventions to improve outcomes for patients with multimorbidity.

Most of the interventions in this review used a conceptual model, particularly the Chronic Care Model. The outcomes chosen should also reflect the theoretical underpinning as to how and why the intervention might work. It would also be helpful if authors clearly identified intervention elements and matched outcomes to these elements in an effort to clarify which components of multifaceted interventions are more effective than others.

Conclusion

This review highlights the paucity of research into interventions to improve outcomes for multimorbidity with the focus to date being on co-morbid conditions or multimorbidity in older patients. It indicates that interventions that are targeted at either specific combinations of common conditions, or at specific problems for patients with multiple conditions, may be more effective. However, further research is needed and future interventions should be developed in ways that allow rigorous evaluations to be performed that will add to the evidence. There is a need for clear and broader definitions of participants, consideration of appropriate outcomes, and further pragmatic studies based in primary care settings.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bogner 2008

Methods	Randomised controlled trial USA
Participants	64 patients aged 50 years and older with hypertension and depression (defined as a diagnosis of depression or prescription of antidepressant within the past year) Integrated care manager and 12 family physicians in primary care clinic
Interventions	Integration of depression and hypertension treatment coordinated by integrated care manager; individualised programcomprising three 30 minute in-person sessions with patients and two 15 minute follow up phone calls
Outcomes	Depression scores (Centre for Epidemiological Studies depression scale (CES-D)); Blood pressure; per cent adherent to antidepressant medication; per cent adherent to antihypertensive medication (adherence measured using electronic measuring devices (MEMS caps)) > or = 80% adherence to antidepressant
Notes	Intervention lasted 6 weeks and follow up 2 weeks later Controls received usual care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states "patients were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated in text
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Automated measurement devices were used but authors don't specifically state that outcome assessors were blinded
Protection against contamination	Low risk	25% control consultations monitored to check for contamination
Reliable primary outcomes	Low risk	Validated measures and automated tests
Follow up of patients	Low risk	100% follow up
Baseline measurement	Low risk	Groups comparable at baseline

Boult 2011

Methods	Cluster randomised controlled trial USA
Participants	904 patients aged 65 years or more with history of high service use and multiple medical conditions, covered by Medicare or other insurance 8 practices with 49 primary care practitioners (PCPs); 7 Guided Care nurses (GCNs) Arranged in 'pods' of 1 GCN, 2-5 PCPs and 50-60 patients
Interventions	'Guided Care' programme comprising eight clinical services including home based assessment, individual management plan, coaching for self-management with monthly monitoring and coordination of care provision Delivered by trained GCNs
Outcomes	PACIC (Patient assessment of chronic illness care) score; Health service use Health care costs (6 months data only available)
Notes	Intervention duration 18 months; follow up at 6 and 18 months Controls received usual care with PCPs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Carried out independently by study statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Interviewers blinded to group allocation
Protection against contamination	Low risk	Cluster design
Reliable primary outcomes	Low risk	Validated measures
Follow up of patients	Low risk	>90%
Baseline measurement	Low risk	Groups comparable at baseline

Eakin 2007

Methods	Randomised controlled trial USA
Participants	Sub-group of 175 Urban Latinos with multimorbidity (defined as two or more chronic conditions) (data on sub-group directly from authors) Bilingual health educator

Eakin 2007 (*Continued*)

Interventions	Diet and physical activity intervention with self-management support delivered by a health educator; involving two face to face visits (60-90 mins) three months apart; three follow up phone calls and three newsletters
Outcomes	Physical activity (Behavioural Risk Factor Surveillance Survey Physical Activity scores); dietary behaviour (Kristal Fat and Fiber Behaviour (FFB) questionnaire); Chronic Illness Resource Survey (CIRS)
Notes	Intervention 16 weeks, follow up 6 months post intervention Control group received usual care plus a guide to local services and three newsletters

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated scheme
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered envelopes used - unclear if were opaque
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated in text
Protection against contamination	Low risk	Not a cluster design but authors state that providers not involved in intervention delivery and intracluster correlation coefficients low previously in this population
Reliable primary outcomes	Low risk	Validated measures used
Follow up of patients	Low risk	80% follow up
Baseline measurement	Low risk	Groups comparable at baseline

Gitlin 2006

Methods	Randomised Controlled Trial USA
Participants	319 patients aged 70 years or more with reported difficulties with at least one activity of daily living
Interventions	Multicomponent home intervention (the ABLE programme) delivered by occupational therapist (OT) and physical therapist (PT) targeted at reducing functional difficulties; involving five OT contacts (4 face to face for 90 minutes and 1 telephone) and one PT visit (90 minutes) over 6 months followed by 6 month follow up with 3 telephone calls

Gitlin 2006 (*Continued*)

	and final home visit Individual priorities identified and strategies such as problem solving, balance and muscle strengthening and fall recovery techniques with use of environmental adjustments where needed
Outcomes	Activities of Daily living (ADLs and IADLs), self-efficacy relating to falls (Falls Efficacy Scale), overall functional self-efficacy, control oriented strategies and presence of home hazards (home hazard index) Mortality (NDI records were obtained for death)
Notes	Intervention lasted 12 months (first 6 months intensive phase followed by second six months telephone contact and final closure visit); data collection at 12 months; mortality data collection 4 years later Usual care comparator with control patients receiving a leaflet on home safety at study completion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation done by project statistician,
Allocation concealment (selection bias)	Low risk	"Randomization lists and four sets of randomisation were prepared using double, opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	"trained interviewers who were masked to group assignment and study hypotheses and who had no role in the intervention interviewed them at 6 and 12 months."
Protection against contamination	Low risk	Control group had no access to intervention
Reliable primary outcomes	Low risk	Self-report outcomes but all validated
Follow up of patients	Low risk	12 month follow up 89%
Baseline measurement	Low risk	Groups comparable at baseline

Hocchalter 2010

Methods	Randomised controlled trial USA
Participants	79 patients aged 65 or older with at least two of seven qualifying chronic illnesses who had received treatment in previous 12 months Primary health care providers in "large Internal Medicine Clinic" in Medical School

Hocchalter 2010 (*Continued*)

	Teaching Hospital
Interventions	Patient engagement intervention: "Making the most of your healthcare" comprising one 2-hour workshop and two follow up phone calls before and after a subsequent routine medical appointment, delivered by 'coaches'
Outcomes	Primary: Patient activation measure (PAM) Secondary: Communication with physicians scale; health-related QoL (HRQOL-14); Self-Efficacy for CDM
Notes	Intervention ran during first 3 months after baseline data collection; follow up at 6 months from baseline Comparison was 'attention control' - workshop on safety in the home Study presented as a feasibility study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Only reported as 'randomly assigned'
Blinding (performance bias and detection bias) All outcomes	Low risk	"interviews carried out by a research assistant blinded to group assignment"
Protection against contamination	Low risk	Control group had no access to patient oriented intervention
Reliable primary outcomes	Low risk	Valid measures used
Follow up of patients	Low risk	81% follow up
Baseline measurement	Low risk	Groups comparable at baseline

Hogg 2009

Methods	Randomised controlled trial Canada
Participants	241 patients aged 50 years or older with at least two chronic conditions and at risk of experiencing adverse health outcomes 8 Family Practitioenrs; 5 nurses and 11 administrative staff in one family health network in rural Ontario
Interventions	APTCare Intervention: Home-based multidisciplinary team management with an initial; assessment by a nurse practitioner and a medication review by pharmacist and individualised patient care plan

Hogg 2009 (*Continued*)

Outcomes	Primary: Chronic disease management score (CDM score) based on 12 indicators for one of four chronic diseases Secondary outcomes: Clinical outcomes where applicable: BP and Hba1c; quality of preventive care using 6 preventive indicators from the Canadian Task Force on Preventive Health Care (Quality of preventive care score); health related QOL scores (SF36); instrumental activities of daily living (IADL score); and health service use (hospitalisation, ED visits)
Notes	Intervention duration 15 months, follow up at intervention completion Controls received usual care

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Done centrally through automated telephone system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unclear for primary outcome, reported as done for secondary outcomes
Protection against contamination	Unclear risk	Potential contamination as not cluster randomised Only intervention patients received intervention but FPs and existing nurses could have modified their behaviour with control patients based on their experience with intervention patients
Reliable primary outcomes	Unclear risk	Unclear for primary outcome Required chart review which was carried out by a physician, where the data was not clearly recorded in the chart, a nurse double checked and they reached agreement No reporting of assessment of process
Follow up of patients	Low risk	95% follow up
Baseline measurement	Low risk	Groups comparable at baseline

Katon 2010

Methods	Randomised controlled trial USA
Participants	214 patients with depression and diabetes and/or coronary heart disease Primary Care Practitioners (PCPs) in 14 primary care clinics and 3 trained medically supervised nurses
Interventions	TEAMcare intervention integrating a treat-to-target programme with structured visits with nurses, individualised care plans and treatment targets, support for self-care combined with pharmacotherapy, provision of self-care materials for patients, weekly meetings to discuss case progression between nurses, PCPs, psychiatrist and psychologist, electronic registry used to track patient risk factors and depression scores
Outcomes	Primary outcome: Composite measure of risk factor control incorporating HBA1c; LDL cholesterol, SBP and scores on the SCL-20 depression scale Secondary outcomes: SCL-20 depression scores; patient global rating of improvement score (i.e. >50% improvement in SCL-20 score); medication adjustments; medication adherence; adherence with diet and exercise plans; quality of life and satisfaction with care
Notes	Control group had "Enhanced primary care' i.e. usual care plus PCPs informed of depression diagnosis and of results at baseline, 6 and 12 months; intervention duration 12 months; follow up data collection at 12 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly assigned by a centrally randomised process"
Allocation concealment (selection bias)	Low risk	Carried out centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	"research assistants who were unaware of the intervention status implemented study procedures"
Protection against contamination	Unclear risk	Control group did not have access to study nurses but managed by same group of PCPs as intervention group
Reliable primary outcomes	Low risk	Automated measures or validated scales
Follow up of patients	Low risk	12 month follow up > 83% all measures, majority > 90%
Baseline measurement	Low risk	Comparable groups at baseline

Krska 2001

Methods	Randomised controlled trial UK
Participants	332 patients aged over 65 years with at least two chronic conditions and taking at least four prescribed medications regularly; six general practices in Grampian, UK
Interventions	Pharmaceutical care plan drawn up by a pharmacist based on medical records and patient interviews, and then implemented by the practice team
Outcomes	Pharmaceutical care issues (PCI scale); SF36 scores Health service utilisation including GP and practice nurse contacts, OPD attendance, use of social services and hospital admissions Direct monthly costs of prescribed medications per patient
Notes	Study duration and follow up 3 months; controls had review of drug therapy by pharmacist but no pharmaceutical care plan implemented

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Text simply states "patients were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Randomisation method not specified
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Protection against contamination	High risk	Authors state that contamination of control patients could have occurred but stated that a cluster design would have been more problematic due to differential prescribing patterns between practices
Reliable primary outcomes	Unclear risk	PCIs previously used but unclear whether validated as outcome measure
Follow up of patients	Low risk	87% follow up
Baseline measurement	Low risk	Some baseline imbalance between groups for PCIs and admissions; not clinically significant

Lorig 1999

Methods	Randomised controlled trial USA
Participants	Subgroup of 536 patients over 40 years with at least two of the following chronic conditions: heart disease, lung disease, stroke or arthritis; recruited through mass media Volunteer lay leaders ran weekly group meetings
Interventions	Chronic Disease Self Management Programme: weekly meetings for seven weeks delivered in community settings by trained volunteer lay leaders
Outcomes	Self-rated health scale (from the National Health Interview Survey); Health Assessment Questionnaire (HAQ) disability scale; psychological well-being (MHI-5 well-being scale) ; pain and physical discomfort scale (adaptation of the Medical Outcomes Survey (MOS) pain scale); energy and fatigue scale (MOS energy and fatigue scale) health distress scale (modified MOS health distress scale); Measures of health behaviour including duration exercise taken, use of cognitive symptom management, communication with physicians, social and role activity limitations Health service utilisation including physician, emergency department and hospital visits and number nights as hospital inpatient Direct programme costs and savings
Notes	Study duration and follow up 6 months; waiting list controls

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study reports "randomisation was conducted serially"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors blinded
Protection against contamination	Low risk	Controls on waiting list so no exposure to those delivering community based intervention
Reliable primary outcomes	Low risk	Validated measures used
Follow up of patients	Unclear risk	Not stated specifically for multimorbidity subgroup; overall follow up 85%
Baseline measurement	Low risk	Groups comparable at baseline

Sommers 2000

Methods	Cluster randomised controlled trial USA
Participants	543 patients older than 65 years with at least two chronic conditions and living independently, attending 18 private office practices of primary care physicians
Interventions	Senior Care Connections (SCC) intervention delivered by a team including the primary care physician, a nurse with geriatric medicine training and a social worker Home visit assessment followed by team discussion and development of a risk reduction plan and treatment targets
Outcomes	Physical functioning (Health activities questionnaire (HAQ)); emotional functioning (short form geriatric depression scale (GDS)); perceived health status (SF36); social activities count; symptom scale; medication count and nutrition checklist Health service utilisation including office, emergency room and home care visits, hospital admissions, skilled nursing facility admissions, length of hospital stay and nursing home placements Direct costs of the intervention
Notes	Study duration 2 years, 12 month follow up post completion intervention; controls received usual care from their primary care physician

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study reports "physicians randomised"
Allocation concealment (selection bias)	Unclear risk	Unclear at cluster level but no bias at patient level as recruited through clusters
Blinding (performance bias and detection bias) All outcomes	Low risk	Healthcare utilisation measured from automated data.
Protection against contamination	Low risk	Cluster randomisation
Reliable primary outcomes	Low risk	Automated data used and validated measures used
Follow up of patients	Low risk	86% follow up for service use measures; 74% follow up questionnaire data
Baseline measurement	Low risk	Groups comparable at baseline

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Addolorato 2004	Specialist setting
Brand 2004	Specialist setting
Dorr 2008	No appropriate data for sub-group with multimorbidity
Drake 1998	Specialist setting
Essock 2006	Specialist setting
Harpole 2005	Intervention not based on multimorbidity: the study presents an analysis of whether co-morbidity alters response to a depression intervention
Hien 2004	Specialist setting
Katon 2004	Intervention directed at one condition only (depression)
Leveille 1998	Participants not defined as having multimorbidity as per review protocol
Lewis 2008	Study design ineligible
Lin 2003	Intervention directed at one condition only (depression)
Lyles 2003	Participants had medically unexplained symptoms, not multimorbidity
Morey 2006	Participants defined as having a range of chronic conditions (from 0-15) with no sub-group eligible for inclusion in this review
Rucker-Whitaker	Study design ineligible
Schneider 2008	Study design and intervention ineligible
Van Eijk 2004	Pilot study only with no follow up
Zhang 2008	Did not meet EPOC criteria for study design

Characteristics of ongoing studies *[ordered by study ID]*

Rosenman 2006

Trial name or title	The Indiana Chronic Disease Management Program
Methods	Randomised Controlled Trial (cluster)
Participants	State-wide programme
Interventions	Seven components: (1) identification of eligible participants to create regional registries, (2) risk stratification of eligible participants, (3) nurse care management for high risk participants, (4) telephonic intervention for all participants, (5) an internet-based information system, (6) quality improvement collaboratives for primary care practices, and (7) program evaluation
Outcomes	Health service utilisation; costs; disease outcomes such as HBA1c for diabetes
Starting date	July 1st 2003
Contact information	mrosenman@iupui.edu
Notes	

Schraeder 2005

Trial name or title	Managing elders with comorbidities
Methods	Prospective, longitudinal randomised treatment-control design
Participants	677 patients aged 65 and older judged to be 'high risk'
Interventions	Primary care based nurse case management
Outcomes	Health care utilisation
Starting date	unclear
Contact information	cheryls@uic.edu
Notes	

Van Bastelaar 2008

Trial name or title	Web-based cognitive behavioural therapy (W-CBT) for diabetes patients with co-morbid depression
Methods	Randomised controlled trial
Participants	286 patients

Interventions	8-week, moderated self-help course tailored to the needs of persons living with diabetes and offered on an individual basis Participants receive feedback on their homework assignments by e-mail from their coach
Outcomes	Primary outcomes are depressive symptoms and diabetes-specific emotional distress. Secondary outcomes are satisfaction with the course, perceived health status, self-care behaviours, glycaemic control, and days in bed/ absence from work
Starting date	Protocol published in 2008
Contact information	k.vanbastelaar@vumc.nl
Notes	

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Intervention elements

Intervention element	**Study (Predominant element of intervention in Bold)**
1. Professional	
Education/ training of care coordinators	Boult, Katon, Sommers
2. Financial	
3. Patient	
Self management support and patient education	Eakin, Boult, Gitlin, Katon, **Lorig, Hochhalter**
Peer support	Lorig
4. Organisational	
4.1 Provider	
Care coordination or management	**Bognor, Boult, Katon,** Sommers
Enhanced multidisciplinary team (e.g. addition pharmacist or social worker)	**Hogg**, Katon, **Krska, Sommers**
4.2 Patient	
Individual care plans	Bognor, Boult, Gitlin, Hogg, Katon, Krska, Sommers
Enhanced multidisciplinary community care	**Eakin, Gitlin**,
4.3 Structural	
Structured visits	Eakin, Bognor, Boult, Gitlin, Hogg, Katon, Krska
Structured telephone contact	Bognor, Eakin, Gitlin, Hochhalter, Hogg
5. Regulatory	

Table 2. Summary of outcomes

Outcome category	Outcome	No. studies with this outcome	Multimorbidity (MM) Vs Co-morbidity (Co-M)*	No. studies with p< 0. 05 for this outcome
Physical Health (6 studies)	Hb1Ac	2	MM and Co-M	1
	BP	3	MM and Co-M	2
	Cholesterol	1	Co-M	1
	Other symptom score	2	MM	0
	Mortality	1	MM	1
Mental Health (4 studies)	Depression scores	3	MM and 2 Co-M	2
	% improved depression	1	Co-M	1
	Cognitive symptom management	1	MM	0
Psychosocial (8 studies)	QoL/ general health	5	4 MM and Co-M	1
	Functional impairment & disability	4	MM	0
	Social (activity/ support)	3	MM	1
	Self efficacy	2	MM	1
	Home hazards	1	MM	0
Health service use (5 studies)	Visits/ use service	4	MM and 1 Co-M	0
	Hospital admission related	5	MM and 1 Co-M	2
Patient health related behaviours (5 studies)	Exercise/ diet	5	MM and 1 Co-M	1
Medication adherence (1 study)		1	Co-M	1

Table 2. Summary of outcomes (*Continued*)

Provider behaviour (4 studies)	Prescribing	2	MM and Co-M	2
	Disease management	2	MM	2
Costs	Direct costs	5	-	Not applicable

* Multimorbidity is defined as two or more independent conditions within the same individual whereas co-morbidity refers to linked conditions. In this review co-morbidity studies included depression and diabetes or depression and hypertension

** The scales or meaurements used in each study for the outcomes are described in the Table of included studies

Table 3. Physical Health Outcomes

Study	Study type	Outcomes	Results	Notes
Bognor	RCT	Systolic BP	Int (n=32): 127.3 (SD 17.7) Con (n= 32): 141.3 (SD 18.8) Absol diff 14 Rel % diff 10%	* SES = 1.12
Bognor	RCT	Diastolic BP	Int (n=32): 83 (SD 10.7) Con (n=32) : 81.4 (SD 11.1) Absol diff 9.2 Rel % diff 11%	* SES = 0.8
Gitlin	RCT	Mortality	Int (n= 160): (0.056) Con (n= 159): (0.132) Absol diff 7.6% Rel% diff 58%	*
Hogg	RCT	Systolic BP	Int (n= 87): 124.3 Con (n= 80): 124. 2 Absol diff 0.1 Rel % diff <0.1%	ns
Hogg	RCT	HBA1c	Int (n= 36): 7.01 Con (n= 36): 6.78 Absol diff 0.23 Rel % diff 3%	ns
Katon	RCT	Systolic BP	Int (n= 105): 131 (SD 18.4) Con (n= 106): 132.3 (SD 17.2) Absol diff 1.3 Rel % diff 1%	* SES = 0.07
Katon	RCT	HBA1c	Int (n= 105): 8.14 (SD 2.03) Con (n= 106): 8.04 (SD 1.87) Absol diff 0.1 Rel % diff 13%	* SES = 0.32

Table 3. Physical Health Outcomes (*Continued*)

Katon	RCT	Cholesterol	Int (n= 105): 91.9 (SD 36.7) Con (n= 106): 101.4 (SD 36.6) Absol diff 9.5 Rel % diff 9%	* SES = 0.26
Lorig	RCT	Pain/ physical discomfort	Int (n= 311) 59.8 (SD 20.1) Con (n= 225) 60.6 (SD 17.1) Absol diff 0.8 Rel %diff 1%	SES = 0.04 ns
Lorig	RCT	Energy/fatigue	Int (n= 311): 2.18 (SD 0.73) Con (n= 225): 2.02 (SD 0.75) Absol diff 0.16 Rel %diff 8%	ns
Lorig	RCT	Shortness of breath	Int (n= 311): 1.34 (SD 0.91) Con (n= 225): 1.58 (SD 0.83) Absol diff 0.24 Rel % diff 15%	ns
Sommers	RCT	Symptom scores	Int (n**): 17.2 Con (n**): 18.9 Absol diff 1.7 Rel % diff 9%	ns

* refers to whether original study reported statistically significant improvement in this outcome
** Total number with final data collected was 384. No final numbers of intervention and control patients presented.

Table 4. Mental Health Outcomes

Study	Study type	Outcome	Result	Notes
Bognor	RCT	CES-depression score	Int: 9.9 (SD10.7) Con 19.3 (SD 15.2) Absol diff 9.4 Rel % diff 49%	* SES = 0.75
Katon	RCT	SCL 20 depression score	Int:0.83 (SD 0.66) Con: 1.14 (SD 0.68) Absol diff 0.31 Rel % diff 27%	* SES = 0.46
Katon	RCT	Patient global improvement in depression	Int: 41/92 Con: 16/91 Absol diff 27% Rel % diff 150%	*

Table 4. Mental Health Outcomes (*Continued*)

Lorig	RCT	Cognitive symptom management score	Int: 1.75 Con: 0.98 Absol diff 0.77 Rel % diff 79%	ns
Sommers	RCT	GDS score (depression)	Int: 4.1 Con: 4.1 Absol diff 0 Rel % diff 0%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 5. Psychosocial outcomes

Study	Study type	Outcome	Result	Notes
Eakin	RCT	Multilevel support for healthy lifestyle	Int: 2.7 Con: 2.59 Absol diff 0.11 Rel % diff 4%	ns
Hochhalter	RCT	Total unhealthy days	Int: 15.3 Con: 14.1 Absol diff 1.2 Rel % diff 9%	ns
Hochhalter	RCT	Self-efficacy	Int: 7.4 Con: 8.0 Absol diff 0.6 Rel % diff 7.5%	ns
Hogg	RCT	Total unhealthy days	Int: 7.6 Con: 9.9 Absol diff 2.3 Rel % diff 23%	ns
Hogg	RCT	SF 36 Mental Health	Int: 52.4 Con:52.2 Absol diff 0.2 Rel % diff 0.3%	ns
Hogg	RCT	SF 36 Physical Health	Int: 44.3 Con:41.5 Absol diff 2.8 Rel % diff 6.7%	ns
Hogg	RCT	IADL	Int: 10.6 Con: 10.9 Absol diff 0.3 Rel % diff 2.7%	ns
Katon	RCT	QoL score	Int: 6.0 (SD 2.2) Con: 5.2 (SD 1.9) Absol diff 0.8	* SES = 0.44

Table 5. Psychosocial outcomes (*Continued*)

			Rel % diff 15%	
Lorig	RCT	Self-rated health	Int: 3.42 Con: 3.44 Absol diff 0.02 Rel %diff 0.6%	ns
Lorig	RCT	Disability	Int: 0.86 Con: 0.96 Absol diff 0.1 Rel %diff 10%	ns
Lorig	RCT	Social role/activity limitation	Int: 1.91 Con: 1.98 Absol diff 0.07 Rel %diff 4%	ns
Lorig	RCT	Psychological well-being	Int: 3.47 Con: 3.33 Absol diff 0.04 Rel %diff 4%	ns SES=0.21
Lorig	RCT	Health distress	Int: 1.97 Con: 2.13 Absol diff 0.16 Rel %diff 7.5%	ns SES=0.16
Sommers	RCT	SF36 score	Int: 2.2 Con: 3.3 Absol diff 1.1 Rel %diff 33%	ns
Sommers	RCT	Social activities count	Int: 8.7 Con: 8.6 Absol diff 0.1 REl %diff 1%	* (when adjusted for baseline diff)
Sommers	RCT	HAQ score	Int: 0.44 Con: 0.5 Absol diff 0.06 Rel %diff 12%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 6. Health service use

Study	Study type	Outcome	Result	Notes
Boult	RCT	No. hospital admissions	Int: 0.7 Con: 0.72 Absol diff 0.02 Rel % diff 3%	ns
Boult	RCT	No. days in hospital	Int: 4.26 Con: 4.49 Absol diff 0.23 Rel % diff 5%	ns
Boult	RCT	No. ED visits	Int: 0.44 Con:0.44 Absol diff 0 Rel % diff 0	ns
Boult	RCT	No. PC visits	Int: 9.98 Con: 9.88 Absol diff 0.1 Rel % diff 1%	ns
Boult	RCT	No. specialist visits	Int 9.04 Con:8.49 Absol diff 0.55 Rel % diff 6%	ns
Boult	RCT	No. home healthcare episodes	Int: 0.99 Con: 1.3 Absol diff 0.31 Rel % diff 24%	*
Hogg	RCT	No. hospital admissions	Int: 0.4 Con: 0.46 Absol diff 0.06 Rel % diff 13%	ns
Hogg	RCT	Proportion hospitalised	Int: 0.26 Con: 0.26 Absol diff 0 Rel % diff 0%	ns
Hogg	RCT	No. ED visits	Int: 0.63 Con: 0.73 Absol diff 0.01 Rel % diff 14%	ns
Hogg	RCT	Proportion with ED visit	Int: 0.38 Con: 0.42 Absol diff 0.04 Rel % diff 9%	ns
Katon	RCT	Proportion hospitalised	Int: 0.26 Con: 0.22 Absol diff 0.04 Rel %diff 18%	ns

Table 6. Health service use (*Continued*)

Lorig	RCT	No. doctor and ED visits	Int: 6.51 Con: 7.08 Absol diff 0.57 Rel %diff 8%	ns
Lorig	RCT	No. hospital stays in past 6 months	Int: 0.26 Con 0.31 Absol diff 0.05 Rel %diff 6%	*
Lorig	RCT	No. nights in hospital in last 6 months	Int: 1.3 Con: 1 Absol diff 0.3 Rel %diff 30%	*
Sommers	RCT	No. hospital admissions per patient per year	Int: 0.36 Con: 0.52 Absol diff 0.16 Rel %diff 31%	*
Sommers	RCT	≥1 60 day readmission	Int 3.6 Con: 9.4 Absol diff 5.8 Rel%diff 62%	*
Sommers	RCT	≥ 1 hospital admission	Int: 8.8 Con: 7.7 Absol diff 1.1 Rel %diff 14%	*
Sommers	RCT	No. PCP visits	Int: 6.0 Con: 6.1 Absol diff 0.1 Rel %diff 2%	ns
Sommers	RCT	No. office visits	Int: 11 Con: 12.5 Absol diff 1.5 Rel %diff 12%	*
Sommers	RCT	≥ 1 home care visit	Int: 19.5 Con: 18.8 Absol diff 0.7 Rel %diff 4%	ns
Sommers	RCT	No. medical specialist visits	Int: 1.4 Con: 1.7 Absol diff 0.3 Rel %diff 18%	ns

Table 6. Health service use (*Continued*)

Sommers	RCT	No. other visits	Int 3.9 Con: 4.3 Absol diff 0.4 Rel %diff 9%	*
Sommers	RCT	≥ 1 ED visit	Int: 21.4 Con: 16.7 Absol diff 4.7 Rel %diff	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 7. Medication adherence

Study	Study type	Outcome	Results	Notes
Bognor	RCT	≥80% adherence to antidepressant medication (MEMS caps)	Int: 23/32 Con: 10/32 Absol diff 0.41 Rel %diff 132%	*
Bognor	RCT	≥80% adherence to antihypertensive medication (MEMS caps)	Int: 25/32 Con: 10/32 Absol diff 0.47 Rel %diff 152%	*

* refers to whether original study reported statistically significant improvement in this outcome

Table 8. Health related patient behaviours

Study	Study type	Outcome	Results	Notes
Hochhalter	RCT	PAM (patient activation measure)	Int: 66.8 Con: 66.2 Absol diff 0.6 Rel % diff 1%	ns
Eakin	RCT	Diet behaviour scores	Int: 2.2 Con: 2.41 Absol diff 0.21 Rel % diff 9%	*
Eakin	RCT	Change minutes of walking/week	Int: +8 Con: -10 Absol diff 18 Rel % diff 180%	*

Table 8. Health related patient behaviours (*Continued*)

Katon	RCT	General adherence to diet score	Int:0.86 Con: 0.81 Absol diff 0.05 Rel % diff 6%	ns
Katon	RCT	General adherence to exercise score	Int: 0.54 Con: 0.44 Absol diff 0.1 Rel % diff 23%	ns
Lorig	RCT	Exercise: stretching and strengthening (mins/week)	Int: 53.1 Con: 40.4 Absol diff 12.7 Rel % diff 31%	ns
Lorig	RCT	Exercise: aerobic (mins/week)	Int: 101.8 Con: 88 Absol diff 13.8 Rel %diff 157%	ns
Lorig	RCT	Communication with doctor (score 1-5)	Int:3.34 Con: 3.2 Absol diff 0.14 Rel %diff 4%	ns
Sommers	RCT	Nutrition checklist score	Int:2.0 Con:1.9 Absol diff 0.1 Rel %diff 5%	ns

* refers to whether original study reported statistically significant improvement in this outcome

Table 9. Provider behaviour

Study	Study type	Outcome	Result	Notes
Boult	RCT	PACIC score (patient measure of quality of care received)	Int: 3.14 Con: 2.85 Absol diff 0.29 Rel % diff 10%	*
Hogg	RCT	Chronic Disease Mangement Score	Int: 0.84 Con: 0.77 Absol diff 0.07 Rel % diff 9%	*
Hogg	RCT	Preventive Care Score	Int: 0.89 Con: 0.7 Absol diff 0.19 Rel % diff 27%	*

Table 9. Provider behaviour (*Continued*)

Krska	RCT	% Pharmaceutical care issues resolved from baseline	Int: 950/1206 Con: 542/1380 Absol diff 0.4 Rel% diff 102%	*

* refers to whether original study reported statistically significant improvement in this outcome

Table 10. Costs

Study	Study type	Outcome	Result	Notes
Boult	RCT	Total healthcare cost	Saving of $75,000 per GCN and $1364 per patient	$ in 2007 Initial result only ns
Katon	RCT	Mean cost per patient	$1224 per patient	$ over 12 month intervention period in late 2000s
Krska	RCT	Mean cost of medicines	Int: 38.83 Con: 42.61 Absol diff 3.78 Rel %diff 9%	£ in 2000 ns SES=0.13
Lorig	RCT	Intervention cost per completed participant	$70	$ in 1998 See text for assumptions made
Lorig	RCT	Cost savings per patient	$750	$ in 1998 See text for assumptions made
Sommers	RCT	Savings per patient	$90	$ in 1994 See text for assumptions made

* refers to whether original study reported statistically significant improvement in this outcome

APPENDICES

Appendix 1. MEDLINE search strategies 2007, 2009, 2011

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to 2011>

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1 Comorbidity/ (48809)
2 (comorbid$ or co-morbid$).ti,ab. (52767)
3 (multimorbid$ or multi-morbid$).ti,ab. (712)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (1619)
5 or/1-4 (88625)
6 Chronic disease/ (196972)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (172333)
8 or/6-7 (329439)
9 5 or 8 (408710)
10 exp diabetes mellitus/ or diabet$.ti,ab. (368459)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (316662)
12 exp heart diseases/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (882594)
13 exp cerebrovascular disorders/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (315505)
14 exp asthma/ or asthma$.ti,ab. (118910)
15 exp pulmonary disease chronic obstructive/ or (copd or (pulmonary adj2 (disease? or disorder?))).ti,ab. (45836)
16 exp hyperlipidemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (65312)
17 exp Thyroid diseases/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (115901)
18 exp arthritis rheumatoid/ or rheumatoid arthritis.ti,ab. (103792)
19 exp mental disorders/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (971649)
20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (142567)
21 exp hiv infections/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis))).ti,ab. (255123)
22 exp neoplasms/ or (neoplasm? or cancer?).ti,ab. (2345120)
23 exp kidney diseases/ or (kidney adj (disease? or disorder?)).ti,ab. (363164)
24 exp liver diseases/ or (liver adj (disease? or disorder?)).ti,ab. (387359)
25 exp osteoporosis/ or osteoporosis.ti,ab. (50531)
26 or/10-25 (5831119)
27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (35702)
28 chronic$.ti,ab,hw. (816669)
29 27 or 28 (847460)

30 26 and 29 (490847)

31 exp *education, continuing/ (27307)
32 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (34430)
33 (behavio?r$ adj2 intervention?).tw. (5300)
34 *pamphlets/ (1206)
35 (leaflet? or booklet? or poster or posters).tw. (17194)
36 ((written or printed or oral) adj information).tw. (1190)
37 (information$ adj2 campaign).tw. (314)
38 (education$ adj1 (method? or material?)).tw. (3637)
39 *advance directives/ (2523)

40 outreach.tw. (5976)
41 ((opinion or education$ or influential) adj1 leader?).tw. (705)
42 facilitator?.tw. (9507)
43 academic detailing.tw. (256)
44 consensus conference?.tw. (3391)
45 *guideline adherence/ (6574)
46 practice guideline?.tw. (10290)
47 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (2446)
48 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (440)
49 *reminder systems/ (915)
50 reminder?.tw. (5184)
51 (recall adj2 system$).tw. (324)
52 (prompter? or prompting).tw. (3472)
53 algorithm?.tw. (93991)
54 *feedback/ or feedback.tw. (64356)
55 chart review$.tw. (16348)
56 ((effect? or impact or records or chart?) adj2 audit).tw. (630)
57 compliance.tw. (64556)
58 marketing.tw. (13755)
59 or/31-58 (373569)

60 exp *reimbursement mechanisms/ (14807)
61 fee for service.tw. (2797)
62 *capitation fee/ (1957)
63 *"deductibles and coinsurance"/ (514)
64 cost shar$.tw. (924)
65 (copayment? or co payment?).tw. (973)
66 (prepay$ or prepaid or prospective payment?).tw. (3894)
67 *hospital charges/ (750)
68 formular?.tw. (2408)
69 fundhold?.tw. (1)
70 *medicaid/ (8711)
71 *medicare/ (15463)
72 blue cross.tw. (992)
73 or/60-72 (44643)
74 *nurse clinicians/ (5175)
75 *nurse midwives/ (4229)
76 *nurse practitioners/ (9690)
77 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (8545)
78 *pharmacists/ (5519)
79 clinical pharmacist?.tw. (974)
80 paramedic?.tw. (2649)
81 *patient care team/ (17606)
82 exp *patient care planning/ (20139)
83 (team? adj2 (care or treatment or assessment or consultation)).tw. (7516)
84 (integrat$ adj2 (care or service?)).tw. (5080)
85 (care adj2 (coordinat$ or program$ or continuity)).tw. (14512)
86 (case adj1 management).tw. (6240)
87 exp *ambulatory care facilities/ (21896)
88 *ambulatory care/ (13520)
89 or/74-88 (125028)
90 *home care services/ (17652)
91 *hospices/ (2988)

92 *nursing homes/ (17447)
93 *office visits/ (1775)
94 *house calls/ (1130)
95 *day care/ (2710)
96 *aftercare/ (2459)
97 *community health nursing/ (13879)
98 (chang$ adj1 location?).tw. (270)
99 domiciliary.tw. (2007)
100 (home adj1 treat$).tw. (1189)
101 day surgery.tw. (1709)
102 *medical records/ (14865)
103 *medical records systems, computerized/ (11752)
104 (information adj2 (management or system?)).tw. (20386)
105 *peer review/ (2810)
106 *utilization review/ (2436)
107 exp *health services misuse/ (2615)
108 or/90-107 (112686)
109 *physician's practice patterns/ (18585)
110 quality assurance.tw. (15565)
111 *process assessment/ [health care] (1134)
112 *program evaluation/ (5726)
113 *length of stay/ (5765)
114 (early adj1 discharg$).tw. (1797)
115 discharge planning.tw. (1848)
116 offset.tw. (14530)
117 triage.tw. (6909)
118 exp *"Referral and Consultation"/ and "consultation"/ (16242)
119 *drug therapy, computer assisted/ (878)
120 near patient testing.tw. (167)
121 *medical history taking/ (3920)
122 *telephone/ (3648)
123 (physician patient adj (interaction? or relationship?)).tw. (1671)
124 *health maintenance organizations/ (9206)
125 managed care.tw. (15056)
126 (hospital? adj1 merg$).tw. (337)
127 or/109-126 (118024)
128 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (25123)
129 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (30065)
130 (program$ adj1 (health or care or intervention?)).tw. (23187)
131 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (257)
132 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (115)
133 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (406)
134 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (340)
135 (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. (3150)
136 ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. (1953)
137 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (1177)
138 or/128-137 (76105)
139 or/59,73,89,108,127,138 (763155)
140 randomized controlled trial.pt. (303682)
141 controlled clinical trial.pt. (82106)
142 random$.ti,ab. (541169)
143 (control$ adj2 (trial? or study or studies)).ti,ab. (205818)
144 double-blind method/ or random allocation/ or single-blind method/ (184152)

145 ((double or single or triple or treble) adj2 blind$).ti,ab. (107156)
146 (quasi-experiment$ or quasiexperiment$).ti,ab. (3965)
147 interrupt$ time series.ti,ab. (571)
148 or/140-147 (839267)

Search Results MEDLINE 2011
149 9 and 139 and 148 (4834)
150 30 and 139 and 148 (3564)
151 149 or 150 [FINAL RESULTS] (6142)
152 limit 151 to yr="2009 -Current" (1334)
153 (2009* or 2010* or 2011*).ed,ep,dp. [Date Limits] (2360220)
154 (or/149-150) and 153 (1510)
155 152 or 154 (1510) [Results 2009 to 2011]

Search Results MEDLINE 2009

149 9 and 139 and 148 (1664)
150 9 and 139 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (2852)
151 30 and 139 and 148 (1125)
152 30 and 139 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (1822)
153 149 or 151 (2043) [Results before year limits]
154 limit 153 to (humans and yr="2008 - 2009") (468)
155 150 or 152 (3409)
156 limit 155 to (humans and yr="2008 - 2009") (787)
157 remove duplicates from 156 (467) [Set 1: 2008-2009]
158 156 or 152 (3409)
159 limit 158 to (humans and yr="2008 - 2009") (787)
160 159 not 157 (564) [Set 2: 2008-2009]

Database: Ovid MEDLINE(R) <1950 to January Week 3 2007>

1 (chronic adj (disease? or illness$ or care)).tw. (20969)
2 Comorbidity/ (27090)
3 (comorbid$ or co-morbid$).tw. (25216)
4 (multimorbid$ or multi-morbid$).tw. (412)
5 exp diabetes mellitus/ (203288)
6 exp hypertension/ (160279)
7 exp heart diseases/ (637458)
8 exp cerebrovascular disorders/ (186988)
9 exp asthma/ (78092)
10 exp pulmonary disease chronic obstructive/ or (chronic adj2 obstructive adj2 pulmonary).tw. (26538)
11 exp thyroid diseases/ (93440)
12 exp hyperlipidemia/ (43072)
13 exp arthritis rheumatoid/ (81863)
14 exp mental disorders/ (637448)
15 exp substance-related disorders/ or exp substance abuse/ (159869)
16 exp epilepsy/ (93966)
17 exp hiv infections/ (158869)
18 exp neoplasms/ (1778994)
19 exp kidney diseases/ (305680)
20 exp liver diseases/ (308939)
21 exp osteoporosis/ (29011)
22 or/1-21 (4309303)
23 exp Primary Health Care/ (45790)

24 Physicians, Family/ (10609)
25 Family Practice/ (49656)
26 exp Community Health Services/ (346548)
27 (primary adj2 care).tw. (43606)
28 ((general or family) adj pract$).tw. (46963)
29 or/23-28 (457523)
30 22 and 29 (141530)
31 exp *education, continuing/ (23228)
32 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (22659)
33 (behavio?r$ adj2 intervention?).tw. (2940)
34 *pamphlets/ (1013)
35 (leaflet? or booklet? or poster or posters).tw. (11881)
36 ((written or printed or oral) adj information).tw. (808)
37 (information$ adj2 campaign).tw. (202)
38 (education$ adj1 (method? or material?)).tw. (2536)
39 *advance directives/ (2061)
40 outreach.tw. (3639)
41 ((opinion or education$ or influential) adj1 leader?).tw. (376)
42 facilitator?.tw. (6416)
43 academic detailing.tw. (150)
44 consensus conference?.tw. (2451)
45 *guideline adherence/ (3729)
46 practice guideline?.tw. (6014)
47 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (1598)
48 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (278)
49 *reminder systems/ (557)
50 reminder?.tw. (3314)
51 (recall adj2 system$).tw. (243)
52 (prompter? or prompting).tw. (2127)
53 algorithm?.tw. (46160)
54 *feedback/ or feedback.tw. (41492)
55 chart review$.tw. (9673)
56 ((effect? or impact or records or chart?) adj2 audit).tw. (448)
57 compliance.tw. (47206)
58 marketing.tw. (9523)
59 or/31-58 (238366)
60 exp *reimbursement mechanisms/ (12118)
61 fee for service.tw. (2172)
62 *capitation fee/ (1883)
63 *"deductibles and coinsurance"/ (411)
64 cost shar$.tw. (584)
65 (copayment? or co payment?).tw. (573)
66 (prepay$ or prepaid or prospective payment?).tw. (3505)
67 *hospital charges/ (598)
68 formular?.tw. (1823)
69 fundhold?.tw. (1)
70 *medicaid/ (7518)
71 *medicare/ (13478)
72 blue cross.tw. (882)
73 or/60-72 (37422)
74 *nurse clinicians/ (4463)
75 *nurse midwives/ (3985)
76 *nurse practitioners/ (8022)

77 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (6622)
78 *pharmacists/ (4022)
79 clinical pharmacist?.tw. (655)
80 paramedic?.tw. (1918)
81 *patient care team/ (14109)
82 exp *patient care planning/ (16742)
83 (team? adj2 (care or treatment or assessment or consultation)).tw. (5202)
84 (integrat$ adj2 (care or service?)).tw. (3085)
85 (care adj2 (coordinat$ or program$ or continuity)).tw. (10081)
86 (case adj1 management).tw. (4686)
87 exp *ambulatory care facilities/ (18216)
88 *ambulatory care/ (11098)
89 or/74-88 (98447)
90 *home care services/ (15097)
91 *hospices/ (2657)
92 *nursing homes/ (14890)
93 *office visits/ (1345)
94 *house calls/ (866)
95 *day care/ (2479)
96 *aftercare/ (2135)
97 *community health nursing/ (12518)
98 (chang$ adj1 location?).tw. (166)
99 domiciliary.tw. (1684)
100 (home adj1 treat$).tw. (914)
101 day surgery.tw. (1309)
102 *medical records/ (13462)
103 *medical records systems, computerized/ (7928)
104 (information adj2 (management or system?)).tw. (13965)
105 *peer review/ (2508)
106 *utilization review/ (2302)
107 exp *health services misuse/ (2058)
108 or/90-107 (92011)
109 *physician's practice patterns/ (12061)
110 quality assurance.tw. (12097)
111 *process assessment/ [health care] (829)
112 *program evaluation/ (3705)
113 *length of stay/ (4521)
114 (early adj1 discharg$).tw. (1385)
115 discharge planning.tw. (1487)
116 offset.tw. (9503)
117 triage.tw. (4147)
118 exp *"Referral and Consultation"/ and "consultation"/ (13190)
119 *drug therapy, computer assisted/ (616)
120 near patient testing.tw. (135)
121 *medical history taking/ (3244)
122 *telephone/ (3062)
123 (physician patient adj (interaction? or relationship?)).tw. (1211)
124 *health maintenance organizations/ (8981)
125 managed care.tw. (13505)
126 (hospital? adj1 merg$).tw. (308)
127 or/109-126 (89787)
128 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (13514)
129 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (19670)

130 (program$ adj1 (health or care or intervention?)).tw. (15915)
131 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (202)
132 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (89)
133 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (310)
134 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (224)
135 (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. (2210)
136 ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. (1074)
137 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (707)
138 or/128-137 (47148)
139 59 or 73 or 89 or 108 or 127 or 138 (539518)
140 randomized controlled trial.pt. (227480)
141 controlled clinical trial.pt. (73834)
142 intervention studies/ (3363)
143 experiment$.tw. (823731)
144 (time adj series).tw. (6024)
145 (pre test or pretest or posttest or post test).tw. (7407)
146 random allocation/ (56614)
147 intervention?.tw. (231845)
148 evaluation studies/ (116150)
149 comparative study.pt. (1305975)
150 or/140-149 (2480883)
151 animal/ (3964641)
152 human/ (9515859)
153 151 not (151 and 152) (3014465)
154 150 not 153 (1767123)
155 30 and 139 and 154 (10979)
156 limit 155 to review (1156)
157 155 not 156 (9823)
158 meta-analysis.pt. (14191)
159 157 not 158 (9776) [2007 MEDLINE Search Results]

Appendix 2. EMBASE Search Strategy 2009, 2011

Database: EMBASE Classic+EMBASE <1947 to 2011 April 07>
1 Comorbidity/ (82841)
2 (comorbid$ or co-morbid$).ti,ab. (69356)
3 (multimorbid$ or multi-morbid$).ti,ab. (1069)
4 (multidisease? or multi-disease? or (multiple adj (ill$ or disease? or condition? or syndrom$ or disorder?))).ti,ab. (2003)
5 or/1-4 (114644)
6 Chronic disease/ (136264)
7 (chronic$ adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or syndrom$ or symptom$)).ti,ab. (226486)
8 or/6-7 (324583)
9 5 or 8 (428959)
10 exp diabetes mellitus/ or diabet$.ti,ab. (541521)
11 exp hypertension/ or (hypertens$ or "high blood pressure?").ti,ab. (521511)
12 exp heart disease/ or exp myocardial disease/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?).ti,ab. (1267000)
13 cerebrovascular disease/ or carotid artery disease/ or ((cerebrovascular or vascular or carotoid$ or arter$) adj (disorder? or disease?)).ti,ab. (170311)
14 exp asthma/ or asthma$.ti,ab. (182043)
15 Chronic Obstructive Lung Disease/ or (copd or ((pulmonary or lung?) adj2 (disease? or disorder?))).ti,ab. (112836)

16 exp hyperlipidemia/ or exp hypercholesterolemia/ or (hyperlipidem$ or Hypercholesterolemia$ or hypertriglyceridemia$).ti,ab. (103018)
17 exp Thyroid disease/ or ((thyroid adj (disease? or disorder)) or hyperthyroid$ or hypothyroid$).ti,ab. (176510)
18 exp rheumatoid arthritis/ or rheumatoid arthritis.ti,ab. (142292)
19 exp mental disease/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren$ or psychos$ or "substance abuse" or addiction?).ti,ab. (1557080)
20 exp epilepsy/ or (epileps$ or seizure?).ti,ab. (203785)
21 Human Immunodeficiency Virus/ or (HIV or acquired immune$ deficiency syndrome? or (aids adj (associated or related or arteritis)) or human immunodeficiency).ti,ab. (240745)
22 exp neoplasm/ or (neoplasm? or cancer?).ti,ab. (3120478)
23 exp kidney disease/ or ((kidney? or renal) adj (disease? or disorder? or failure)).ti,ab. (610122)
24 exp liver disease/ or (liver adj (disease? or disorder?)).ti,ab. (598717)
25 exp osteoporosis/ or osteoporosis.ti,ab. (83134)
26 or/10-25 (7896479) [CHRONIC DISEASES]

27 ((coocur$ or co-ocur$ or coexist$ or co-exist$ or multipl$) adj3 (disease? or ill$ or care or condition? or disorder$ or health$ or medication$ or symptom$ or syndrom$)).ti,ab. (49330)
28 chronic$.ti,ab,hw. (1069293)
29 27 or 28 (1112010) [COMORBIDITY KW]

30 26 and 29 (679455)

31 exp primary health care/ or exp primary medical care/ (81649)
32 (primary adj2 (care? or medical$ or health$ or clinic$ or practitioner? or doctor?)).ti,ab. (85021)
33 General practitioner/ (49989)
34 (((family or general or generalist? or communit$) adj2 (physician? or doctor? or practitioner? or practice)) or GP).ti,ab. (121960)
35 General Practice/ (64045)
36 exp Community Care/ (85297)
37 (communit$ adj2 (health or healthcare or service? or clinic$ or setting? or centre? or center?)).ti,ab. (42367)
38 or/31-37 (362774) [PRIMARY/COMMUNITY CARE]

39 (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. (41473)
40 (behavio?r$ adj2 intervention?).tw. (6575)
41 (leaflet? or booklet? or poster or posters).tw. (21974)
42 ((written or printed or oral) adj information).tw. (1610)
43 (information$ adj2 campaign).tw. (376)
44 (education$ adj1 (method? or material?)).tw. (4967)
45 outreach.tw. (6722)
46 ((opinion or education$ or influential) adj1 leader?).tw. (810)
47 facilitator?.tw. (11340)
48 academic detailing.tw. (325)
49 consensus conference?.tw. (4389)
50 practice guideline?.tw. (12316)
51 (guideline? adj2 (introduc$ or issu$ or impact or effect? or disseminat$ or distribut$)).tw. (3162)
52 ((introduc$ or impact or effect? or implement$ or computer$ or compli$) adj2 protocol?).tw. (2901)
53 ((introduc$ or impact or effect? or implement$ or computer$ or compli$) adj2 algorithm?).tw. (4415)
54 clinical pathway?.tw. (1837)
55 critical pathway?.tw. (1063)
56 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. (541)
57 reminder?.tw. (6421)
58 (recall adj2 system$).tw. (379)
59 (prompter? or prompting).tw. (4238)

60 advance directive?.tw. (2383)
61 *feedback/ or feedback.tw. (77098)
62 chart review$.tw. (20152)
63 ((effect? or impact or records or chart?) adj2 audit).tw. (732)
64 compliance.tw. (85055)
65 marketing.tw. (17272)
66 ((cost or clinical or medical) adj information).tw. (16932)
67 *medical education/ (88351)
68 *medical audit/ (7236)
69 continuing education/ (24259)
70 postgraduate education/ (10841)
71 or/39-70 (454670)
72 fee for service.tw. (3250)
73 cost shar$.tw. (1072)
74 (copayment? or co payment?).tw. (1190)
75 (prepay$ or prepaid or prospective payment?).tw. (4606)
76 formular?.tw. (3596)
77 fundhold?.tw. (1)
78 blue cross.tw. (1270)
79 voucher?.tw. (784)
80 (free adj2 care).tw. (989)
81 exp *health insurance/ (76709)
82 *health care costs/ (22888)
83 *health care financing/ (2898)
84 *medical fee/ (3754)
85 *prospective payment/ (3600)
86 or/72-85 (111711)
87 (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. (9599)
88 ((nurse or midwi$ or practitioner) adj managed).tw. (483)
89 clinical pharmacist?.tw. (1511)
90 paramedic?.tw. (2967)
91 exp *paramedical personnel/ (150569)
92 *general practitioner/ (12680)
93 *physician/ (39648)
94 (team? adj2 (care or treatment or assessment or consultation)).tw. (9621)
95 (integrat$ adj2 (care or service?)).tw. (6230)
96 (care adj2 (coordinat$ or program$ or continuity)).tw. (17458)
97 (case adj1 management).tw. (7143)
98 *patient care/ (35434)
99 (chang$ adj1 location?).tw. (322)
100 domiciliary.tw. (2995)
101 (home adj1 (treat$ or visit?)).tw. (6036)
102 day surgery.tw. (2312)
103 exp *primary health care/ (32665)
104 *ambulatory surgery/ (5447)
105 *nursing home/ (20222)
106 *day hospital/ (1295)
107 *outpatient care/ (2584)
108 *terminal care/ (11841)
109 *group practice/ (5508)
110 *general practice/ (35609)
111 *rural health care/ (5461)
112 *community mental health center/ (1890)

113 information system/ (28190)
114 *medical record/ (30370)
115 (information adj2 (management or system?)).tw. (24521)
116 *peer review/ (4866)
117 *professional standards review organization/ (1497)
118 exp *clinical practice/ (19402)
119 quality assurance.tw. (19729)
120 exp *health care delivery/ (390497)
121 *health care quality/ (50102)
122 *professional practice/ (16218)
123 (early adj1 discharg$).tw. (2299)
124 discharge planning.tw. (2049)
125 offset.tw. (16637)
126 triage.tw. (8148)
127 near patient testing.tw. (209)
128 *patient referral/ (10832)
129 (physician patient adj (interaction? or relationship?)).tw. (1870)
130 managed care.tw. (17248)
131 *health care organization/ (37240)
132 *health maintenance organization/ (8550)
133 *health care system/ (10198)
134 *health care access/ (4001)
135 (hospital? adj1 merg$).tw. (374)
136 (computer$ adj2 (dosage or dosing or diagnosis therapy or decision?)).tw. (1218)
137 (computer$ adj2 (diagnosis or therapy)).tw. (2589)
138 gatekeep$.tw. (2510)
139 or/87-138 (948412)
140 ((standard or usual or routine or regular or traditional or conventional or pattern) adj2 care).tw. (31677)
141 (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. (36983)
142 (program$ adj1 (health or care or intervention?)).tw. (27734)
143 ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. (1452)
144 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. (349)
145 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. (134)
146 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. (495)
147 ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. (388)
148 or/140-147 (87770)
149 71 or 86 or 139 or 148 (1459644)
150 randomized controlled trial/ or controlled clinical trial/ or clinical trial/ or controlled study/ (3959072)
151 random$.ti,ab. (658367)
152 (control$ adj2 (trial? or study or studies)).ti,ab. (253170)
153 ((double or single or triple or treble) adj2 blind$).ti,ab. (138000)
154 (quasi-experiment$ or quasiexperiment$).ti,ab. (4424)
155 interrupt$ time series.ti,ab. (655)
156 or/150-155 (4289901)

EMBASE 2009 Search Results

157 9 and 38 and 149 and 156 (1647)
158 9 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (1104)
159 30 and 38 and 149 and 156 (1209)
160 30 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (817)
161 157 or 159 (2040)
162 limit 161 to human (2007)
163 158 or 160 (1340)
164 limit 163 to human (1265)

EMBASE 2011 Search Results
157 9 and 38 and 149 and 156 (2770)
158 9 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (2477)
159 30 and 38 and 149 and 156 (1969)
160 30 and 38 and 149 and (intervent$.ti,ab,pt. or evaluat$.ti,hw. or impact$.ti.) (1710)
161 157 or 159 (3348)
162 (2009* or 2010* or 2011*).em. (2420210)
163 (2009* or 2010* or 2011*).dp. (401327)
164 161 and (or/162-163) (920)

Appendix 3. CAB Abstracts Strategy 2009, 2011

CAB Abstracts Search Strategy 2007 to 05-01-2009

	S7	S2 and S6	**Interface** - EBSCOhost **Search Screen** - Advanced Search **Database** - CAB Abstracts; **Expanders** - Apply related words **Search modes** - Boolean/Phrase (87)
	S6	AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or or economic* or outcome*) or SU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or DU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or poli-	**Limiters** - Publication Year from: 2007-2009; Broad Category: Human Sciences **Search modes** - SmartText Searching (27147)

(*Continued*)

		cies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pre ...Show Less	
S5		AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or SU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or DU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-exper-	**Limiters** - Publication Year from: 2007-2009; Broad Category: Human Sciences **Search modes** - Boolean/Phrase [number of results for this line did not display when screen shot was taken to record this strategy]

(*Continued*)

		iment*“ or control* or random* or ”time series“ or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or ”evidence base*“ or pilot* or quasirandom* or ”quasi-random*“ or quasicontrol* or ”quasi-control*“ or cost* or implement* or ”single blind*“ or ”double blind*“ or ”triple blind*“ or blinded or blinding or economic* or outcome*)AB (”pretest* or “pre-test* or posttest* or ”post-test*“ or quasiexperiment* or ”quasi-experiment*“ or control* or random* or ”time series“ or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or ”evidence base*“ or pilot* or quasirandom* or ”quasi-random*“ or quasicontrol* or ”quasi-control*“ or cost* or implement* or ”single blind*“ or ”double blind*“ or ”triple blind*“ or blinded or blinding or economic* or outcome*)AB (”pretest* or “pre-test* or posttest* or ”post-test*“ or quasiexperiment* or ”quasi-experiment*“ or control* or random* or ”time series“ or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or ”evidence base*“ or pilot* or quasirandom* or ”quasi-random*“ or quasicontrol* or ”quasi-control*“ or cost* or implement* or ”single blind*“ or ”double blind*“ or ”triple blind*“ or blinded or blinding or economic* or outcome*) or TI (”pre ...Show Less	
S4		AB (“pretest* or ”pre-test* or posttest* or “post-test*” or quasiexperiment* or “quasi-experiment*” or control* or random* or “time series” or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or “evidence base*” or pilot* or quasirandom* or “quasi-random*” or quasicontrol* or “quasi-control*” or cost* or implement* or “single blind*” or “double blind*” or “triple blind*” or blinded or blinding or economic* or outcome*) or TI (“pretest* or ”pre-test* or posttest* or “post-test*” or quasiexperiment* or “quasi-experiment*” or control* or random* or “time series” or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or “evidence base*” or pilot* or quasirandom* or “quasi-random*” or quasicontrol* or “quasi-control*” or cost* or implement* or “single blind*” or “double blind*” or “triple blind*” or blinded or blinding or economic* or outcome*) or SU (“pretest* or ”pre-test* or posttest* or “post-test*” or quasiexperiment* or “quasi-experiment*” or control* or random* or “time series” or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or “evidence base*” or pilot* or quasirandom* or “quasi-random*” or quasicontrol* or “quasi-control*” or cost* or implement* or “single blind*” or “double blind*” or “triple blind*” or blinded or blinding or economic* or outcome*) or DU (“pretest* or ”pre-test* or	**Expanders** - Apply related words **Search modes** - SmartText Searching (427444)

(*Continued*)

		posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pre ...Show Less	
S3		AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or SU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding	**Expanders** - Apply related words **Search modes** - Boolean/Phrase [number of results for this line did not display when screen shot was taken to record this strategy]

(*Continued*)

		or economic* or outcome*) or DU ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*)AB ("pretest* or "pre-test* or posttest* or "post-test*" or quasiexperiment* or "quasi-experiment*" or control* or random* or "time series" or before or intervention* or multicenter or multicentre or policy or policies or protocol or guideline* or trial* or "evidence base*" or pilot* or quasirandom* or "quasi-random*" or quasicontrol* or "quasi-control*" or cost* or implement* or "single blind*" or "double blind*" or "triple blind*" or blinded or blinding or economic* or outcome*) or TI ("pre ...Show Less	
	S2	AB ("co-morbid*" or multimorbid*) or TI ("co-morbid*" or multimorbid*) or SU ("co-morbid*" or multimorbid*)	**Limiters** - Publication Year from: 2007-2009; Broad Category: Human Sciences **Expanders** - Apply related words **Search modes** - Boolean/Phrase (315)
	S1	AB ("co-morbid*" or multimorbid*) or TI ("co-morbid*" or multimorbid*) or SU ("co-morbid*" or multimorbid*)	**Expanders** - Apply related words **Search modes** - Boolean/Phrase (804)

Appendix 4. Cochrane Central Register of Controlled Trials Strategy 2009, 2011

Search Name: Multimorbidity 1.2
Comments: 25/05/2011
Save Date: 2011-05-25 12:43:54.87

IDSearch
#1MeSH descriptor Comorbidity, this term only
#2(comorbid* or co-morbid* or multimorbid* or multi-morbid* or multidisease or multidiseases or multi-disease or multi-diseases):ti
#3MeSH descriptor Chronic Disease, this term only
#4(#1 OR #2 OR (#2 AND #3))
#5MeSH descriptor Diabetes Mellitus explode tree 2
#6diabet*:ti,ab

#7MeSH descriptor Hypertension explode all trees
#8(hypertens* or "high blood pressure"):ti,ab
#9MeSH descriptor Heart Diseases explode all trees
#10MeSH descriptor Cerebrovascular Disorders explode tree 1
#11(cerebrovascular disorder* or cerebrovascular disease* or vascular disorder* or vascular disease* or carotoid* disorder* or carotoid disease* or arter* disorder* or arter* disease*):ti
#12MeSH descriptor Asthma explode tree 2
#13asthma*:ti
#14MeSH descriptor Pulmonary Disease, Chronic Obstructive explode all trees
#15(copd or pulmonary disease* or pulmonary disorder*):ti
#16MeSH descriptor Hyperlipidemias explode all trees
#17(hyperlipidem* or Hypercholesterolemia* or hypertriglyceridemia*):ti
#18MeSH descriptor Thyroid Diseases explode all trees
#19(thyroid disease* or thyroid disorder*):ti
#20MeSH descriptor Mental Disorders explode all trees
#21((mental or anxiety or mood or psychological or sleep) NEAR/2 (disease* or disorder*)):ti
#22((substance or drug or marijuana or cocaine or Amphetamine) NEAR/2 abuse):ti
#23(depression or schizophren* or psychos* or "substance abuse" or addiction or addictions):ti
#24MeSH descriptor Epilepsy explode all trees
#25(epileps* or seizure or seizures):ti
#26MeSH descriptor HIV Infections explode tree 1
#27(HIV or acquired immune* deficiency syndrome*):ti
#28MeSH descriptor Neoplasms explode all trees
#29(neoplasm or cancer):ti
#30MeSH descriptor Kidney Diseases explode tree 1
#31(kidney disease* or kidney disorder*):ti
#32MeSH descriptor Liver Diseases explode all trees
#33(liver disease* or liver disorder*):ti
#34MeSH descriptor Osteoporosis explode all trees
#35osteoporosis:ti
#36(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
#37((coocur* or co-ocur* or coexist* or co-exist* or multipl*) NEAR/2 (disease or diseases or ill* or care or condition or conditions or disorder* or health* or medication* or symptom* or syndrom*)):ti,ab
#38(#36 AND #37)
#39(#4 OR #38)

Appendix 5. CINAHL Strategy

	Limiters/Expanders	Last Run Via	Results
S70	S26 or S66 or S67 or S68 or S69	Date from: 20090101-20111231 Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL	1149
S69	S3 AND S51 AND S64	Expanders - Apply related words Search modes - Boolean/Phrase	5313

(*Continued*)

S68	(S24 or S25) AND S51	Expanders - Apply related words Search modes - Boolean/Phrase	378
S67	(S24 or S25) AND S58	Expanders - Apply related words Search modes - Boolean/Phrase	173
S66	S3 and S58	Expanders - Apply related words Search modes - Boolean/Phrase	1781
S65	S59 or S60 or S61 or S62 or S63	Expanders - Apply related words Search modes - Boolean/Phrase	927340
S64	S59 or S60 or S61 or S62 or S63	Expanders - Apply related words Search modes - Boolean/Phrase	927340
S63	MW care or patient or community	Expanders - Apply related words Search modes - Boolean/Phrase	864406
S62	(MH "Community Health Services+")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S61	(MH "Primary Health Care")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S60	(MH "Physicians, Family") or TI (family physician? or family doctor?) or AB (family doctor? or family physician?)	Expanders - Apply related words Search modes - Boolean/Phrase	7946
S59	(MH "Family Practice") or (family practice) or (general practice) or (family practitioner*) or (general practitioner*) or (family doctor*)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S58	S52 or S53 or S54 or S55 or S56 or S57	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S57	TI controlled	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S56	TI ("control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*") or AB ("control* N1 clinical" or "control* N1 group*" or "control* N1 trial*" or "control* N1 study" or "control* N1 studies" or "control* N1 design*" or "control* N1 method*")	Expanders - Apply related words Search modes - Boolean/Phrase	Display

(*Continued*)

S55	TI random* or AB random*	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S54	TI ("clinical study" or "clinical studies") or AB ("clinical study" or "clinical studies")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S53	(MM "Clinical Trials+")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S52	TI ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*)) or AB ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*))	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S51	S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S50	TI ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 "more than")) or AB ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 "more than"))	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S49	TI ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3	Expanders - Apply related words Search modes - Boolean/Phrase	Display

(*Continued*)

	group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study)) or AB ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3 group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study))		
S48	TI (multicentre or multicenter or multi-centre or multi-center) or AB random*	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S47	TI random* OR controlled	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S46	TI (trial or (study n3 aim) or "our study") or AB ((study n3 aim) or "our study")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S45	TI (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop)) or AB (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop))	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S44	TI (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*) or AB (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S43	(intervention n6 clinician*) or (intervention n6 community) or (intervention n6 complex) or (intervention n6 design*) or (intervention n6 doctor*) or (intervention n6 educational) or (intervention n6 family doctor*) or (intervention n6 family physician*) or (intervention n6 family practitioner*) or (intervention n6 financial) or (intervention n6 GP) or (intervention n6 general practice*) Or (intervention n6 hospital*) or (intervention n6 impact*) Or (intervention n6 improv*) or (intervention n6 individualize*) Or (intervention n6 indi-	Expanders - Apply related words Search modes - Boolean/Phrase	Display

(*Continued*)

	vidualise*) or (intervention n6 individualizing) or (intervention n6 individualising) or (intervention n6 interdisciplin*) or (intervention n6 multicomponent) or (intervention n6 multi-component) or (intervention n6 multidisciplin*) or (intervention n6 multi-disciplin*) or (intervention n6 multifacet*) or (intervention n6 multi-facet*) or (intervention n6 multimodal*) or (intervention n6 multimodal*) or (intervention n6 personalize*) or(intervention n6 personalise*) or (intervention n6 personalizing) or (intervention n6 personalising) or (intervention n6 pharmaci*) or (intervention n6 pharmacist*) or (intervention n6 pharmacy) or (intervention n6 physician*) or (intervention n6 practitioner*) Or (intervention n6 prescrib*) or (intervention n6 prescription*) or (intervention n6 primary care) or (intervention n6 professional*) or (intervention* n6 provider*) or (intervention* n6 regulatory) or (intervention n6 regulatory) or (intervention n6 tailor*) or (intervention n6 target*) or (intervention n6 team*) or (intervention n6 usual care)		
S42	TI (collaborativ* or collaboration* or tailored or personalised or personalized) or AB (collaborativ* or collaboration* or tailored or personalised or personalized)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S41	TI pilot	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S40	(MH "Pilot Studies")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S39	AB "before-and-after"	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S38	AB time series	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S37	TI time series	Expanders - Apply related words Search modes - Boolean/Phrase	Display

(*Continued*)

S36	AB (before* n10 during or before n10 after) or AU (before* n10 during or before n10 after)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S35	TI ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*)) or AB ((time point*) or (period* n4 interrupted) or (period* n4 multiple) or (period* n4 time) or (period* n4 various) or (period* n4 varying) or (period* n4 week*) or (period* n4 month*) or (period* n4 year*))	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S34	TI ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*)) or AB ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol* or quasi* W3 method* or quasi* W3 study or quasi* W3 studies or quasi* W3 trial or quasi* W3 design* or experimental W3 method* or experimental W3 study or experimental W3 studies or experimental W3 trial or experimental W3 design*))	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S33	TI pre w7 post or AB pre w7 post	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S32	MH "Multiple Time Series" or MH "Time Series"	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S31	TI ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies) or AB ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies)	Expanders - Apply related words Search modes - Boolean/Phrase	Display

(*Continued*)

S30	MH Experimental Studies or Community Trials or Community Trials or Pretest-Posttest Design + or Quasi-Experimental Studies + Pilot Studies or Policy Studies + Multicenter Studies	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S29	TI (pre-test* or pretest* or posttest* or post-test*) or AB (pre-test* or pretest* or posttest* or "post test*) OR TI (preimplement*" or pre-implement*) or AB (pre-implement* or preimplement*)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S28	TI (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*) or AB (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*)	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S27	(MH "Quasi-Experimental Studies")	Expanders - Apply related words Search modes - Boolean/Phrase	Display
S26	TI (multimorbid* or multi-morbid*) or AB (multimorbid* or multi-morbid*)	Expanders - Apply related words Search modes - Boolean/Phrase	91
S25	s22 and s23	Expanders - Apply related words Search modes - Boolean/Phrase	1504
S24	S6 and S23	Expanders - Apply related words Search modes - Boolean/Phrase	163
S23	TI (coocurr* or coexist* or co-ocurr* or coexist* or co-exist*) or AB (coocurr* or coexist* or co-ocurr* or coexist* or co-exist*)	Expanders - Apply related words Search modes - Boolean/Phrase	2525
S22	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or 21	Expanders - Apply related words Search modes - Boolean/Phrase	654174
S21	TI diabet* or asthma* or chronic or disease	Expanders - Apply related words Search modes - Boolean/Phrase	122978
S20	MW (disease OR diseases) or MW syndrome? or MW chronic	Expanders - Apply related words Search modes - Boolean/Phrase	257724

(*Continued*)

S19	(MM "Kidney Diseases+")	Expanders - Apply related words Search modes - Boolean/Phrase	15581
S18	(MM "Osteoporosis+")	Expanders - Apply related words Search modes - Boolean/Phrase	5571
S17	(MM "Neoplasms+")	Expanders - Apply related words Search modes - Boolean/Phrase	110248
S16	(MM "Liver Diseases+")	Expanders - Apply related words Search modes - Boolean/Phrase	11645
S15	(MM "Human Immunodeficiency Virus+")	Expanders - Apply related words Search modes - Boolean/Phrase	2007
S14	(MH "Mental Disorders, Chronic") OR (MM "Mental Disorders+")	Expanders - Apply related words Search modes - Boolean/Phrase	133504
S13	(MM "Epilepsy+")	Expanders - Apply related words Search modes - Boolean/Phrase	3755
S12	(MM "Arthritis+")	Expanders - Apply related words Search modes - Boolean/Phrase	15603
S11	(MM "Thyroid Diseases+")	Expanders - Apply related words Search modes - Boolean/Phrase	3068
S10	(MM "Lung Diseases, Obstructive+") OR (MM "Pulmonary Disease, Chronic Obstructive+") OR (MM "Asthma+")	Expanders - Apply related words Search modes - Boolean/Phrase	18552
S9	(MM "Cardiovascular Diseases+")	Expanders - Apply related words Search modes - Boolean/Phrase	148585
S8	(MM "Hypertension+") OR (MM "Cerebrovascular Disorders+")	Expanders - Apply related words Search modes - Boolean/Phrase	43901
S7	(MH "Diabetes Mellitus+")	Expanders - Apply related words Search modes - Boolean/Phrase	50346
S6	S4 or S5	Expanders - Apply related words Search modes - Boolean/Phrase	33990
S5	TI (chronic* W3 disease? or chronic* W3 ill* or chronic* W3 care or chronic* W3 condition? or chronic* W3 disorder* or chronic* W3 health* or chronic* W3 medication* or chronic* W3 syndrom* or chronic* W3 symptom*) or AB (chronic* W3 disease? or chronic*	Expanders - Apply related words Search modes - Boolean/Phrase	17703

(*Continued*)

	W3 ill* or chronic* W3 care or chronic* W3 condition? or chronic* W3 disorder* or chronic* W3 health* or chronic* W3 medication* or chronic* W3 syndrom* or chronic* W3 symptom*)		
S4	(MH "Chronic Disease")	Expanders - Apply related words Search modes - Boolean/Phrase	21759
S3	S1 or S2	Expanders - Apply related words Search modes - Boolean/Phrase	25441
S2	TI (multimorbid* or multi-morbid* or comorbid* or co-morbid* or multidisease? or multi-disease?) or AB (multimorbid* or multi-morbid* or comorbid* or co-morbid* or multidisease? or multi-disease?) or TI (multiple N2 ill* or multiple N2 disease? or multiple N2 condition? or multiple N2 syndrom* or multiple N2 disorder?) or AB (multiple N2 ill* or multiple N2 disease? or multiple N2 condition? or multiple N2 syndrom* or multiple N2 disorder?) or TI (coocur* N3 disease? or coocur* N3 ill* or coocur* N3 care or coocur* N3 condition? or coocur* N3 disorder* or coocur* N3 health* or coocur* N3 medication* or coocur* N3 symptom* or coocur* N3 syndrom* or coexist* N3 disease? Or coexist* N3 ill* or coexist* N3 condition? or coexist* N3 disorder* or coexist* N3 symptom* or coexist* N3 syndrom* or multipl* N3 disease? Or multipl* N3 ill* or multipl* N3 condition? or multipl* N3 disorder* or multipl* N3 medication* or multipl* N3 symptom* or multipl* N3syndrom* or co-exist* N3 disease? Or co-exist* N3 ill* or co-exist* N3 condition? or co-exist* N3 disorder* or co-exist* N3 health* co-exist* N3 symptom* or co-exist* N3 syndrom* or co-ocur* N3 disease? Or co-ocur* N3 ill* or co-ocur* N3 condition? or co-ocur* N3 disorder* or co-ocur* N3 health* or co-ocur* N3 symptom* or co-ocur* N3 syndrom*) or AB (coocur* N3 disease? or coocur* N3 ill* or coocur* N3 care or coocur* N3 condition? or coocur*	Expanders - Apply related words Search modes - Boolean/Phrase	14294

(*Continued*)

	N3 disorder* or coocur* N3 health* or coocur* N3 medication* or coocur* N3 symptom* or coocur* N3 syndrom* or coexist* N3 disease? Or coexist* N3 ill* or coexist* N3 condition? or coexist* N3 disorder* or coexist* N3 symptom* or coexist* N3 syndrom* or multipl* N3 disease? Or multipl* N3 ill* or multipl* N3 condition? or multipl* N3 disorder* or multipl* N3 medication* or multipl* N3 symptom* or multipl* N3syndrom* or co-exist* N3 disease? Or co-exist* N3 ill* or co-exist* N3 condition? or co-exist* N3 disorder* or co-exist* N3 health* co-exist* N3 symptom* or co-exist* N3 syndrom* or co-ocur* N3 disease? Or co-ocur* N3 ill* or co-ocur* N3 condition? or co-ocur* N3 disorder* or co-ocur* N3 health* or co-ocur* N3 symptom* or co-ocur* N3 syndrom*)		
S1	(MH "Comorbidity")		

WHAT'S NEW

Last assessed as up-to-date: 7 November 2011.

Date	Event	Description
1 May 2013	Amended	Minor edits, fixed ref for Katon 2010

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2012

Date	Event	Description
24 May 2011	Amended	Search updated Feb 2011
12 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Susan Smith (SS) conceived, co-ordinated, and designed the review.

Hassan Soubhi (HS) helped co-ordinate the review, assessed studies for inclusion, and extracted data from included studies.

Martin Fortin (MF), Catherine Hudon (CH), and Tom O'Dowd (TOD) along with SS and HS contributed to all stages of the protocol and review, and were involved in writing all review drafts and responding to peer review comments.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Health Research Board Primary Care Research Centre, Ireland.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the review process, the authors decided, following a suggestion from a peer reviewer, that interventions should be excluded if they only targeted one condition as this was contrary to the emphasis on multimorbidity. This led to the exclusion of some studies examining co-morbid depression and other conditions where the intervention was only targeted at depression treatment.

Changes were also made to the original search strategy in the protocol, based on initial results from the original searches. The searches used in the review are presented as appendices.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Health Care; Age Factors; Chronic Disease [*therapy]; Community Health Services; Comorbidity; Disease Management; Patient-Centered Care [methods]; Randomized Controlled Trials as Topic; Risk Factors; Treatment Outcome

MeSH check words

Humans