BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011249
Article Type:	Protocol
Date Submitted by the Author:	22-Jan-2016
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice, Pharmacology and therapeutics
Keywords:	Depressive Disorder, Chronic Disease, Disease Management, Systematic Review, Study Protocol

TITLE

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Chronic Diseases: A Protocol for Systematic Review and Meta-Analysis

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KEYWORDS

Depressive Disorder; Chronic Disease; Disease Management; Systematic Review; Study Protocol

WORD COUNT

2489

ABSTRACT

INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic diseases. The growing comorbidity of chronic and mental diseases pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with chronic diseases.

METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials on treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic diseases. Two databases MEDLINE and Cochrane, and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and comorbid physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other "active" intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and/or significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen's d), I^2 and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.

AMENDMENTS

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,[1] thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.[2]

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.[3] This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,[4-5] amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,[6] which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,[7] and stressing the need to develop responsive health services.[8]

It has also been documented that depression is a risk factor for chronic diseases,[9-11] and that it significantly worsens the health[6,12-13] and the prognosis of its sufferers,[14-19] which results in a greater usage rate of health care services[20] and low treatment adherence;[21] likewise, poor health[22] and the presence of chronic diseases are risk factors for depression.[11, 22-23]

The strong link between depression and chronic diseases signals the presence of complex underlying biological mechanisms.[24] Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),[25-26] a rise in metabolic stress,[27-28] increased cellular ageing,[29] and an alteration of innate inflammatory response.[30-33]

These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,[16] rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.[34] In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases[35] and on the reduction of health care costs.[36-37]

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,[38] pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.[39] In this context, the search for effective treatments for depression in people with chronic diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,[40-44] which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases[40-42,44] or on a single type of approach, such as psychoactive drugs.[43,45] In view of the aforementioned, the present systematic

review is intended to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with chronic diseases.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness of the available treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic diseases. In order to do this, the present systematic review and meta-analysis seek to answer the following questions:

1. Which treatments are effective in reducing depressive symptoms in adults with Major Depressive Episodes/Disorder and chronic diseases?
2. Which treatments for Major Depressive Episodes/Disorder in adults with chronic diseases are effective in achieving a response?
3. Which treatments are effective in achieving the remission of Major Depressive Episodes/Disorder in adults with chronic diseases?
4. Which treatments are effective in attaining a significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and chronic diseases?

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRIMSA-P) checklist[46] was used for the publication of the protocol of the present systematic review and meta-analysis.

STUDY ELEGIBILITY CRITERIA

Participants

1. Participant characteristics
   Adults, aged 18 years or older, with no distinction of sex or ethnicity, diagnosed with Major Depressive Episodes/Disorder and one (or more) comorbid chronic physical disease(s).
2. Diagnosis of Major Depression
   The review will only include studies whose participants were diagnosed with Major Depressive Episodes/Disorder using the following standardized criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The diagnosis must have been provided by a qualified individual, either a psychiatrist or another suitably trained health professional.
3. Comorbidities
   Comorbid physical diseases are not the main concern of this review; however, they must be diagnosed using well-established standardized criteria applied by qualified health professionals.
   Patients with one or more of the following conditions will be included: diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV infection, and rheumatic diseases, among others.

Interventions

1. Pharmacological treatment
   Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine),

monoamine oxidase inhibitors (for example, phenelzine), serotonin and norepinephrine reuptake inhibitors (for example, venlafaxine), non classified antidepressants (for example, bupropion), and/or any new antidepressant agents.[52]

2. Psychological therapy
   Any standardized treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of Major Depressive Episode/Disorder and attaining a better level of functioning.[53]
   Treatments can be intended for individuals, families, or groups, in either a face-to-face or distance format, through the use of information and communication technologies.
   These include behavioural, cognitive, humanistic, psychoanalytic, psychodynamic, and/or integrative types of psychotherapy.
3. Psychosocial interventions
   Treatments intended to supply help, education, or orientation to patients concerning Major Depression Episode/Disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace, and monitoring, among others.[54]
4. Any combination of points 1, 2, and 3.

Comparators

1. Comparison between one or more treatments labelled "interventions" by the researchers and which are consistent with the previous section ("interventions").[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of health care, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life.
Further details are included in the section "Outcomes and prioritisation".

Study design

Randomized clinical trials, systematic reviews, or meta-analyses published in the databases defined for the searches.

Context

There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

REPORT ELIGIBILITY CRITERIA
Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

INFORMATION SOURCES
The databases defined as information sources were MEDLINE and Cochrane. The search strategy for both sources is described in the relevant section.
In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

SEARCH STRATEGY
Table 1 includes the search strategies for each information source.

Table 1. Search Strategies	
MEDLINE	(((((("Depression/drug therapy"[Mesh] OR "Depression/nursing"[Mesh] OR "Depression/psychology"[Mesh] OR "Depression/rehabilitation"[Mesh] OR "Depression/therapy"[Mesh]) OR ("Depressive Disorder/diet therapy"[Mesh] OR "Depressive Disorder/drug therapy"[Mesh] OR "Depressive Disorder/nursing"[Mesh] OR "Depressive Disorder/psychology"[Mesh] OR "Depressive Disorder/rehabilitation"[Mesh] OR "Depressive Disorder/therapy"[Mesh])) OR ("depression care"[Title/Abstract] OR ((((((("depression/nursing"[Title/Abstract] OR "depression/psychology"[Title/Abstract]) OR "depression/therapy"[Title/Abstract]) OR "antidepressant"[Title/Abstract]) OR "depression treatment"[Title/Abstract]) OR "depression psychotherapy"[Title/Abstract]) OR "depression counseling"[Title/Abstract]) OR "depression therapy"[Title/Abstract]) OR "depression management"[Title/Abstract]))) AND

	(((((((chronic disease[Title/Abstract] OR "chronic disease"[Title/Abstract]) OR "chronic disease"[MeSH Terms]) OR ("diabetes"[Title/Abstract] OR "diabetes mellitus"[MeSH Terms])) OR ((((((Chronic Respiratory Diseases[Title] OR "Chronic respiratory disease"[Title/Abstract]) OR "Chronic respiratory diseases"[Title/Abstract]) OR "Asthma"[Title/Abstract]) OR Chronic Obstructive Pulmonary Disease[Title/Abstract]) OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) OR "Chronic Obstructive Pulmonary Disease"[Title/Abstract])) OR (("Neoplasms"[Mesh] OR "Neoplasms"[Title/Abstract]) OR "Cancer"[Title/Abstract])) OR ((Cardiovascular Diseases[Title/Abstract] OR "Cardiovascular Diseases"[Mesh]) OR "Cardiovascular Diseases"[Title/Abstract])) OR "HIV Infections"[Mesh] OR "Rheumatic Diseases"[Mesh]))) AND ((("comorbid"[Title/Abstract] OR "comorbidity"[Title/Abstract]) OR "comorbidities"[Title/Abstract]) OR "comorbidity"[MeSH Terms])) AND ((Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND hasabstract[text] AND "2005/08/30"[PDat] : "2015/08/27"[PDat] AND (English[lang] OR Spanish[lang]))
Cochrane	*"depression" AND "chronic" AND "disease" AND "treatment" in Title, Abstract, Keywords , Publication Year from 2005 to 2015* in *Trials*'

STUDY RECORS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, and those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.
Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.
To extract data from the studies selected, and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]
To follow this format, a piloting process will be conducted which will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA, and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion, and the consensual criteria for extracting information will be refined.
After this piloting process, the authors (AC, DA, and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR), will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

DATA ITEMS
Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic disease [if specified], Major Depressive Episode/Disorder, gravity of the symptoms [if specified], and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups), and the main results of the study which are relevant to the review.

OUTCOMES AND PRIORITISATION
Primary outcomes

1. Effectiveness in the reduction of depressive symptoms
   Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among others.
   Timing: not specified. At least two follow-up measures.
2. Treatment response
   A change of over 50% in depression scores on validated questionnaires, compared with baseline scores.
   Timing: not specified. At least two follow-up measures.
3. Remission of Major Depressive Episodes/Disorder

Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.
Timing: not specified. At least two follow-up measures.

Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[61] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[62]
   Timing: not specified. At least two follow-up measures.

RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[63] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material.

No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

DATA SYNTHESIS

In this stage, all the authors (AC, DA, GR, PM, PV) will work together.

A qualitative synthesis of all the studies included will be conducted in order to provide an overview of the effectiveness of treatments for Major Depressive Episodes/Disorder in adults with comorbid chronic diseases.

A meta-analytic methodology will be applied, including a random effects model of the studies with relatively similar characteristics, since it is assumed that multiple sources of heterogeneity will exist (the studies are not identical).[64]

As effect size measures, in each of the selected studies, relative risk (RR) will be calculated for dichotomous outcomes, while the standardized mean difference (SMD) (Cohen's d) between treatment groups will be calculated for continuous data.[65]

In general, the treatments described in the intervention section will be compared with the control condition selected for each study in order to assess their effect on the primary and secondary outcome measures relevant to the present review.

Heterogeneity between randomized clinical trials will be studied by visually inspecting the resulting forest plots and by employing the I^2 and Q statistics.[66] Results will be summarized using the Summary of Findings table recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will include:

a. Reduction in depressive symptoms achieved by the treatments, reported as a continuous outcome measure.
b. Response to treatments for Major Depressive Episodes/Disorder, reported as a dichotomous outcome measure.
c. Remission of Major Depressive Episodes/Disorder achieved by the treatments, reported as a dichotomous outcome measure.
d. Significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and chronic diseases achieved by the treatments, reported as a dichotomous outcome measure.

Subgroup analyses will be conducted by: type of chronic condition, treatment type, and setting.
In addition, a meta-regression will be carried out. In order to do this, the sample will be stratified according to the initial severity of the Major Depressive Episodes/Disorder, which will make it possible to assess the potential differential effect of a treatment in connection with the severity of the disorder.

META-BIAS(ES)
Funnel plots and Egger's test will be used to assess potential publication biases.[67]

CONFIDENCE IN CUMULATIVE EVIDENCE
After presenting this summary of findings, the quality of the whole set of tests for each individual result will be assessed using the GRADE approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This approach considers the following aspects: within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. This approach specifies four levels of quality (high, moderate, low, and very low).

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic Reviews).

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AUTHORS' CONTRIBUTIONS

GR is in charge of the review, of supervising the process, and of providing her expert opinion on the subject. DA, AC, and PM made contributions to the development of the selection criteria and the search strategy, and will be tasked with extracting the data and evaluating the risk of bias. PV provided his statistical and clinical expertise and will help to supervise the process. All the authors contributed equally to the study design, and edited, modified, and approved the final version of the manuscript.

FINANCIAL SUPPORT

This systematic review was financed by the Chilean National Fund for Scientific and Technological Development (FONDECYT), project N°1130230, and the Fund for Innovation and Competitiveness (FIC) of the Chilean Ministry of Economy, Development, and Tourism, through the Millennium Scientific Initiative, Grant N° IS130005.

ROLE OF FUNDERS

Both financial backers are not involved in any other aspect of the project.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form. The authors have no competing interests to disclose.

BMJ Open

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011249.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Jul-2016
Complete List of Authors:	Martínez, Pablo; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Universidad de Santiago de Chile, Information Technology Innovation Centre for Social Applications (CITIAPS) Castro, Ariel; Universidad de Chile, School of Medicine, Faculty of Medicine Alonso, Diego; Universidad de Chile, School of Medicine, Faculty of Medicine Vöhringer, Paul A; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Tufts University, Mood Disorders Program, Tufts Medical Center Rojas, Graciela; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Millenium Institute for Depression and Personality Research (MIDAP)
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice, Pharmacology and therapeutics
Keywords:	Depressive Disorder, Chronic Disease, Disease Management, Systematic Review, Study Protocol

TITLE

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for systematic review and meta-analysis

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KEYWORDS

Depressive Disorder; Chronic Disease; Disease Management; Systematic Review; Study Protocol

WORD COUNT

2536

ABSTRACT

INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic physical diseases. This growing comorbidity pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials. Two databases MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL), and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and chronic physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other “active” intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen’s d), I^2 and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.

AMENDMENTS

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,[1] thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.[2]

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.[3] This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,[4-5] amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,[6] which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,[7] and stressing the need to develop responsive health services.[8]

It has also been documented that depression is a risk factor for chronic physical diseases,[9-11] and that it significantly worsens the health[6,12-13] and the prognosis of its sufferers,[14-19] which results in a greater usage rate of health care services[20] and low treatment adherence;[21] likewise, poor health[22] and the presence of chronic diseases are risk factors for depression.[11, 22-23]

The strong link between depression and chronic physical diseases signals the presence of complex underlying biological mechanisms.[24] Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),[25-26] a rise in metabolic stress,[27-28] increased cellular ageing,[29] and an alteration of innate inflammatory response.[30-33]

These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,[16] rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.[34] In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases[35] and on the reduction of health care costs.[36-37]

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,[38] pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.[39] In this context, the search for effective treatments for depression in people with comorbid chronic physical diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,[40-44] which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases[40-42,44] or on a single type of therapeutic approach, such as psychoactive drugs.[43,45] In view of the aforementioned, the present systematic review is intended to assess the effectiveness of the management of

Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness of the available treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic physical diseases. In order to do this, the present systematic review and meta-analysis seek to answer the following questions:

1. Which treatments are effective in reducing depressive symptoms in adults with Major Depressive Episodes/Disorder and comorbid chronic physical diseases?
2. Which treatments for Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases are effective in achieving a response?
3. Which treatments are effective in achieving the remission of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases?
4. Which treatments are effective in attaining a significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and comorbid chronic physical diseases?

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRIMSA-P) checklist[46] was used for the publication of the protocol of the present systematic review and meta-analysis.

STUDY ELEGIBILITY CRITERIA

Participants

1. Participant characteristics
   Adults, aged 18 years or older, with no distinction of sex or ethnicity, diagnosed with Major Depressive Episodes/Disorder and one (or more) comorbid chronic physical disease(s).
2. Diagnosis of Major Depression
   The review will only include studies whose participants were diagnosed with Major Depressive Episodes/Disorder using the following standardized criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The diagnosis must have been provided by a qualified individual, either a psychiatrist or another suitably trained health professional.
3. Comorbidities
   Comorbid physical diseases are not the main concern of this review; however, they must be diagnosed using well-established standardized criteria applied by qualified health professionals.
   Patients with one or more of the following conditions will be included: diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV infection, rheumatic diseases, and gastrointestinal disease.

Interventions

1. Pharmacological treatment

Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine), monoamine oxidase inhibitors (for example, phenelzine), serotonin and norepinephrine reuptake inhibitors (for example, venlafaxine), non classified antidepressants (for example, bupropion), and/or any new antidepressant agents.[52]

2. Psychological therapy
   Any standardized treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of Major Depressive Episode/Disorder and attaining a better level of functioning.[53]
   Treatments can be intended for individuals, families, or groups, in either a face-to-face or distance format, through the use of information and communication technologies.
   Examples of psychological therapies that may be included are: behavioural, cognitive, interpersonal, among others.
3. Psychosocial interventions
   Treatments intended to supply help, education, or orientation to patients concerning Major Depression Episode/Disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace, and monitoring, among others.[54]
4. Any combination of points 1, 2, and 3.

Comparators

1. Comparison between one or more treatments labelled "interventions" by the researchers and which are consistent with the previous section ("interventions").[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of health care, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life.
Further details are included in the section "Outcomes and prioritisation".

Study design

Randomized clinical trials, systematic reviews, or meta-analyses published in the databases defined for the searches.

Context
There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

REPORT ELIGIBILITY CRITERIA
Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

INFORMATION SOURCES
The databases defined as information sources were MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL). The search strategy for both sources is described in the relevant section.
In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

SEARCH STRATEGY
Table 1 includes the search strategies for each information source.

Table 1. Search Strategies

MEDLINE	1. Depression[Mesh] OR (depress*[Title/Abstract] AND care[Title/Abstract] AND manag*[Title/Abstract]) OR (depress*[Title/Abstract] AND (therapy[Title/Abstract] OR treatment[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR antidepress*[Title/Abstract]) 2. Chronic Disease[Mesh] OR Diabetes Mellitus[Mesh] OR Chronic Obstructive Pulmonary Disease[Mesh] OR Chronic Respiratory Disease[Title/Abstract] OR Ashtma[Title/Abstract] OR Neoplasms[Mesh] OR Cancer[Title/Abstract] OR Cardiovascular Diseases[Mesh] OR HIV Infections[Mesh] OR Rheumatic Diseases[Mesh] OR Gastrointestinal Diseases[Mesh] 3. Randomized Controlled Trial[Publication type] OR Controlled Clinical Trial[Publication Type] OR Random Allocation[Mesh] OR Placebos[Mesh] OR Control Groups[Mesh] OR Clinical Trials As A Topic[Mesh] OR Meta-Analysis[Publication Type] OR Systematic Review[Title/Abstract] 4. #1 AND #2 AND #3
Cochrane Library*	1. [mh “Depression”] OR [mh “Depressive Disorder”] OR ((depress*:ti,ab) AND (care OR manag*):ti,ab) OR ((depress*:ti,ab) AND (therapy OR treatment OR psychotherapy OR counseling OR antidepress*):ti,ab)

	2. [mh “Chronic Disease”] OR [mh “Diabetes Mellitus”] OR [mh “Chronic Obstructive Pulmonary Disease”] OR (“Chronic Respiratory Disease”:ti,ab) OR (Asthma:ti,ab) OR [mh Neoplasms] OR (Cancer:ti,ab) OR [mh “Cardiovascular Diseases”] OR [mh “HIV Infections”] OR [mh “Rheumatic Diseases”] OR [mh “Gastrointestinal Diseases”] 3. #1 AND #2

STUDY RECORS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, and those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.

Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.

To extract data from the studies selected, and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]

To follow this format, a piloting process will be conducted which will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA, and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion, and the consensual criteria for extracting information will be refined.

After this piloting process, the authors (AC, DA, and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR), will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

DATA ITEMS

Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic physical diseases [if specified], Major Depressive Episode/Disorder, gravity of the symptoms [if specified], and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups), and the main results of the study which are relevant to the review.

OUTCOMES AND PRIORITISATION

Primary outcomes

1. Effectiveness in the reduction of depressive symptoms
   Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among others.
   Timing: not specified. At least two follow-up measures.
2. Treatment response
   According to standard definition,[61] a change of over 50% in depression scores on validated questionnaires, compared with baseline scores.
   Timing: not specified. At least two follow-up measures.
3. Remission of Major Depressive Episodes/Disorder
   Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.
   Timing: not specified. At least two follow-up measures.

Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[62] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[63]
   Timing: not specified. At least two follow-up measures.

RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[64] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material. No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

DATA SYNTHESIS

In this stage, all the authors (AC, DA, GR, PM, PV) will work together.
A qualitative synthesis of all the studies included will be conducted in order to provide an overview of the effectiveness of treatments for Major Depressive Episodes/Disorder in adults with chronic physical diseases.
A meta-analytic methodology will be applied, including a random effects model of the studies with relatively similar characteristics, since it is assumed that multiple sources of heterogeneity will exist (the studies are not identical).[65]
As effect size measures, in each of the selected studies, relative risk (RR) will be calculated for dichotomous outcomes, while the standardized mean difference (SMD) (Cohen's d) between treatment groups will be calculated for continuous data.[66]
In general, the treatments described in the intervention section will be compared with the control condition selected for each study in order to assess their effect on the primary and secondary outcome measures relevant to the present review.
Heterogeneity between randomized clinical trials will be studied by visually inspecting the resulting forest plots and by employing the I^2 and Q statistics.[67]
Results will be summarized using the Summary of Findings table recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will include:

a. Reduction in depressive symptoms achieved by the treatments, reported as a continuous outcome measure.
b. Response to treatments for Major Depressive Episodes/Disorder, reported as a dichotomous outcome measure.
c. Remission of Major Depressive Episodes/Disorder achieved by the treatments, reported as a dichotomous outcome measure.
d. Significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and chronic physical diseases achieved by the treatments, reported as a continuous outcome measure.

Subgroup analyses will be conducted by: ethnicity, setting, type of physical chronic condition, psychiatric comorbidities, and treatment type.
In addition, a meta-regression will be carried out. In order to do this, the sample will be stratified according to the initial severity of the Major Depressive Episodes/Disorder, which will make it possible to assess the potential differential effect of a treatment in connection with the severity of the disorder.

META-BIAS(ES)
Funnel plots and Egger's test will be used to assess potential publication biases.[68]

CONFIDENCE IN CUMULATIVE EVIDENCE
After presenting this summary of findings, the quality of the whole set of tests for each individual result will be assessed using the GRADE approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This approach considers the following aspects: within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and

risk of publication bias. This approach specifies four levels of quality (high, moderate, low, and very low).

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic Reviews) and dissemination activities will be targeted to all the health-care providers.

CONTRIBUTORSHIP STATEMENT

GR is in charge of the review, of supervising the process, and of providing her expert opinion on the subject. DA, AC, and PM made contributions to the development of the selection criteria and the search strategy, and will be tasked with extracting the data and evaluating the risk of bias. PV provided his statistical and clinical expertise and will help to supervise the process. All the authors contributed equally to the study design, and edited, modified, and approved the final version of the manuscript.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form. The authors have no competing interests to disclose.

FUNDING

This systematic review was financed by the Chilean National Fund for Scientific and Technological Development (FONDECYT), project N°1130230; the Fund for Innovation and Competitiveness (FIC) of the Chilean Ministry of Economy, Development, and Tourism, through the Millennium Scientific Initiative, Grant N° IS130005; and the Program for Institutional Improvement – Universidad de Santiago de Chile (PMI USA 1204) of the Ministry of Education, through the Information Technology Innovation Centre for Social Applications (CITIAPS). Financial backers are not involved in any other aspect of the project.

DATA SHARING STATEMENT

No additional data available.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011249.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2016
Complete List of Authors:	Martínez, Pablo; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Universidad de Santiago de Chile, Information Technology Innovation Centre for Social Applications (CITIAPS) Castro, Ariel; Universidad de Chile, School of Medicine, Faculty of Medicine Alonso, Diego; Universidad de Chile, School of Medicine, Faculty of Medicine Vöhringer, Paul A; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Tufts University, Mood Disorders Program, Tufts Medical Center Rojas, Graciela; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Millenium Institute for Depression and Personality Research (MIDAP)
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Evidence based practice, Pharmacology and therapeutics
Keywords:	Depressive Disorder, Chronic Disease, Disease Management, Systematic Review, Study Protocol

TITLE

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for a systematic review and meta-analysis

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KEYWORDS

Depressive Disorder; Chronic Disease; Disease Management; Systematic Review; Study Protocol

WORD COUNT

2536

ABSTRACT

INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic physical diseases. This growing comorbidity pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials. Two databases MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL), and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and chronic physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other “active” intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen’s d), I^2 and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.
- Effects of physical conditions will not be taken into account, possibly affecting the rates of depression and the estimation of treatment effect.

AMENDMENTS

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,[1] thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.[2]

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.[3] This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,[4-5] amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,[6] which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,[7] and stressing the need to develop responsive health services.[8]

It has also been documented that depression is a risk factor for chronic physical diseases,[9-11] and that it significantly worsens the health[6,12-13] and the prognosis of its sufferers,[14-19] which results in a greater usage rate of health care services[20] and low treatment adherence;[21] likewise, poor health[22] and the presence of chronic diseases are risk factors for depression.[11, 22-23]

The strong link between depression and chronic physical diseases signals the presence of complex underlying biological mechanisms.[24] Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),[25-26] a rise in metabolic stress,[27-28] increased cellular ageing,[29] and an alteration of innate inflammatory response.[30-33]

These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,[16] rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.[34] In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases[35] and on the reduction of health care costs.[36-37]

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,[38] pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.[39] In this context, the search for effective treatments for depression in people with comorbid chronic physical diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,[40-44] which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases[40-42,44] or on a single type of therapeutic approach, such as psychoactive drugs.[43,45] In view of the aforementioned, the present systematic review is intended to assess the effectiveness of the management of

Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness of the available treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic physical diseases. In order to do this, the present systematic review and meta-analysis seek to answer the following questions:

1. Which treatments are effective in reducing depressive symptoms in adults with Major Depressive Episodes/Disorder and comorbid chronic physical diseases?
2. Which treatments for Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases are effective in achieving a response?
3. Which treatments are effective in achieving the remission of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases?
4. Which treatments are effective in attaining a significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and comorbid chronic physical diseases?

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRIMSA-P) checklist[46] was used for the publication of the protocol of the present systematic review and meta-analysis.

STUDY ELEGIBILITY CRITERIA

Participants

1. Participant characteristics
   Adults, aged 18 years or older, with no distinction of sex or ethnicity, diagnosed with Major Depressive Episodes/Disorder and one (or more) comorbid chronic physical disease(s).
2. Diagnosis of Major Depression
   The review will only include studies whose participants were diagnosed with Major Depressive Episodes/Disorder using the following standardized criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The diagnosis must have been provided by a qualified individual, either a psychiatrist or another suitably trained health professional.
3. Comorbidities
   Comorbid physical diseases are not the main concern of this review; however, they must be diagnosed using well-established standardized criteria applied by qualified health professionals.
   Patients with one or more of the following conditions will be included: diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV infection, rheumatic diseases, and gastrointestinal disease.

Interventions

1. Pharmacological treatment

Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine), monoamine oxidase inhibitors (for example, phenelzine), serotonin and norepinephrine reuptake inhibitors (for example, venlafaxine), non classified antidepressants (for example, bupropion), and/or any new antidepressant agents.[52]

2. Psychological therapy
   Any standardized treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of Major Depressive Episode/Disorder and attaining a better level of functioning.[53]
   Treatments can be intended for individuals, families, or groups, in either a face-to-face or distance format, through the use of information and communication technologies.
   Examples of psychological therapies that may be included are: behavioural, cognitive, interpersonal, among others.
3. Psychosocial interventions
   Treatments intended to supply help, education, or orientation to patients concerning Major Depression Episode/Disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace, and monitoring, among others.[54]
4. Any combination of points 1, 2, and 3.

Comparators

1. Comparison between one or more treatments labelled "interventions" by the researchers and which are consistent with the previous section ("interventions").[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of health care, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life.
Further details are included in the section "Outcomes and prioritisation".

Study design

Randomized clinical trials, systematic reviews, or meta-analyses published in the databases defined for the searches.

Context
There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

REPORT ELIGIBILITY CRITERIA
Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

INFORMATION SOURCES
The databases defined as information sources were MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL). The search strategy for both sources is described in the relevant section.
In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

SEARCH STRATEGY
Table 1 includes the search strategies for each information source.

Table 1. Search Strategies

MEDLINE	1. Depression[Mesh] OR (depress*[Title/Abstract] AND care[Title/Abstract] AND manag*[Title/Abstract]) OR (depress*[Title/Abstract] AND (therapy[Title/Abstract] OR treatment[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR antidepress*[Title/Abstract]) 2. Chronic Disease[Mesh] OR Diabetes Mellitus[Mesh] OR Chronic Obstructive Pulmonary Disease[Mesh] OR Chronic Respiratory Disease[Title/Abstract] OR Ashtma[Title/Abstract] OR Neoplasms[Mesh] OR Cancer[Title/Abstract] OR Cardiovascular Diseases[Mesh] OR HIV Infections[Mesh] OR Rheumatic Diseases[Mesh] OR Gastrointestinal Diseases[Mesh] 3. Randomized Controlled Trial[Publication type] OR Controlled Clinical Trial[Publication Type] OR Random Allocation[Mesh] OR Placebos[Mesh] OR Control Groups[Mesh] OR Clinical Trials As A Topic[Mesh] OR Meta-Analysis[Publication Type] OR Systematic Review[Title/Abstract] 4. #1 AND #2 AND #3
Cochrane Library*	1. [mh “Depression”] OR [mh “Depressive Disorder”] OR ((depress*:ti,ab) AND (care OR manag*):ti,ab) OR ((depress*:ti,ab) AND (therapy OR treatment OR psychotherapy OR counseling OR antidepress*):ti,ab)

	2. [mh “Chronic Disease”] OR [mh “Diabetes Mellitus”] OR [mh “Chronic Obstructive Pulmonary Disease”] OR (“Chronic Respiratory Disease”:ti,ab) OR (Asthma:ti,ab) OR [mh Neoplasms] OR (Cancer:ti,ab) OR [mh “Cardiovascular Diseases”] OR [mh “HIV Infections”] OR [mh “Rheumatic Diseases”] OR [mh “Gastrointestinal Diseases”] 3. #1 AND #2

STUDY RECORS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, and those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.

Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.

To extract data from the studies selected, and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]

To follow this format, a piloting process will be conducted which will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA, and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion, and the consensual criteria for extracting information will be refined.

After this piloting process, the authors (AC, DA, and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR), will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

DATA ITEMS

Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic physical diseases [if specified], Major Depressive Episode/Disorder, gravity of the symptoms [if specified], and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups), and the main results of the study which are relevant to the review.

OUTCOMES AND PRIORITISATION

Primary outcomes

1. Effectiveness in the reduction of depressive symptoms
   Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among others.
   Timing: not specified. At least two follow-up measures.
2. Treatment response
   According to standard definition,[61] a change of over 50% in depression scores on validated questionnaires, compared with baseline scores.
   Timing: not specified. At least two follow-up measures.
3. Remission of Major Depressive Episodes/Disorder
   Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.
   Timing: not specified. At least two follow-up measures.

Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[62] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[63]
   Timing: not specified. At least two follow-up measures.

RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[64] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material. No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

DATA SYNTHESIS

In this stage, all the authors (AC, DA, GR, PM, PV) will work together.
A qualitative synthesis of all the studies included will be conducted in order to provide an overview of the effectiveness of treatments for Major Depressive Episodes/Disorder in adults with chronic physical diseases.
A meta-analytic methodology will be applied, including a random effects model of the studies with relatively similar characteristics, since it is assumed that multiple sources of heterogeneity will exist (the studies are not identical).[65]
As effect size measures, in each of the selected studies, relative risk (RR) will be calculated for dichotomous outcomes, while the standardized mean difference (SMD) (Cohen's d) between treatment groups will be calculated for continuous data.[66]
In general, the treatments described in the intervention section will be compared with the control condition selected for each study in order to assess their effect on the primary and secondary outcome measures relevant to the present review.
Heterogeneity between randomized clinical trials will be studied by visually inspecting the resulting forest plots and by employing the I^2 and Q statistics.[67]
Results will be summarized using the Summary of Findings table recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will include:

a. Reduction in depressive symptoms achieved by the treatments, reported as a continuous outcome measure.
b. Response to treatments for Major Depressive Episodes/Disorder, reported as a dichotomous outcome measure.
c. Remission of Major Depressive Episodes/Disorder achieved by the treatments, reported as a dichotomous outcome measure.
d. Significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and chronic physical diseases achieved by the treatments, reported as a continuous outcome measure.

Subgroup analyses will be conducted by: ethnicity, setting, type of physical chronic condition, psychiatric comorbidities, and treatment type.
In addition, a meta-regression will be carried out. In order to do this, the sample will be stratified according to the initial severity of the Major Depressive Episodes/Disorder, which will make it possible to assess the potential differential effect of a treatment in connection with the severity of the disorder.

META-BIAS(ES)
Funnel plots and Egger's test will be used to assess potential publication biases.[68]

CONFIDENCE IN CUMULATIVE EVIDENCE
After presenting this summary of findings, the quality of the whole set of tests for each individual result will be assessed using the GRADE approach, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[56] This approach considers the following aspects: within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and

risk of publication bias. This approach specifies four levels of quality (high, moderate, low, and very low).

DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic Reviews) and dissemination activities will be targeted to all the health-care providers.

CONTRIBUTORSHIP STATEMENT

GR is in charge of the review, of supervising the process, and of providing her expert opinion on the subject. DA, AC, and PM made contributions to the development of the selection criteria and the search strategy, and will be tasked with extracting the data and evaluating the risk of bias. PV provided his statistical and clinical expertise and will help to supervise the process. All the authors contributed equally to the study design, and edited, modified, and approved the final version of the manuscript.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form. The authors have no competing interests to disclose.

FUNDING

This systematic review was financed by the Chilean National Fund for Scientific and Technological Development (FONDECYT), project N°1130230; the Fund for Innovation and Competitiveness (FIC) of the Chilean Ministry of Economy, Development, and Tourism, through the Millennium Scientific Initiative, Grant N° IS130005; and the Program for Institutional Improvement – Universidad de Santiago de Chile (PMI USA 1204) of the Ministry of Education, through the Information Technology Innovation Centre for Social Applications (CITIAPS). Financial backers are not involved in any other aspect of the project.

DATA SHARING STATEMENT

No additional data available.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported in page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.