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Pharmacological management of depression in patients with an inadequate first-line treatment response: a systematic review of clinical practice guidelines

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ABSTRACT

Objective We assessed the most relevant clinical practice guidelines (CPGs) for the pharmacological treatment of depression differ for adults who respond inadequately to first-line treatment.

Data Sources We performed a systematic review of the literature spanning January 2011 to August 2020 in Medline, Embase, Cochrane, and 12 databases recognized as guideline repositories. CPG quality was assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE) II.

Study Selection Only CPGs that made pharmacological recommendations for treating depression in primary and secondary care for individuals aged 18 years or older were included.

Data Extraction Two independent researchers extracted all recommendations for patients who did not respond to first-line pharmacological treatment from the selected CPGs. This process included extracting the quality of the evidence and the strength of the recommendation.

Results Of the 8 CPGs included, 5 were of high-quality (≥ 80% in domain 3 of AGREE II), 2 were recognized as clinically relevant, and 1 was created by an institution with experience developing guidelines. Less than half the guidelines defined an adequate response to treatment and mentioned a clear sequence of strategies in clinical practice. The timeline to declare that patients did not respond adequately was found to be unclear.

Conclusions An inadequate response to the pharmacological treatment of depression must be better defined in the guidelines, which commonly differ in recommendations for nonresponsive patients, mainly in their recommended sequence of strategies. Future guideline developers must address these concerns to improve healthcare provision.

Strengths and limitations of this study

- The inclusion of two guidelines often used in clinical practice enabled a broader discussion of clinical questions mentioned in the clinical practice guidelines.
- The study benefitted from a comprehensive literature search and careful training of our appraisers.
- However, this study only employed English, Portuguese, or Spanish papers in its analysis.
- Moreover, the study employed AGREE II as an assessment method, thereby acquiring its inherent subjectivity in assessing quality.

INTRODUCTION

Depression is a mental health problem with severe consequences for afflicted individuals. This mental disorder results in substantial professional, economic, social, and personal losses for affected individuals owing to its incapacitating nature.[1] The World Health Organization[2] estimates that over 300 million people globally are affected by depression, which is the main contributor to 800,000 suicides annually worldwide. Additionally, depression can cause important social problems, as depressed individuals are less productive, resulting in additional costs to their employers and governments.[3]

Along with an increasingly aging population, the number of depressed persons has increased considerably.[4] This situation overburdens the healthcare system and generates a greater need for resource optimization.[5] Thus, the development of evidence-based interventions to achieve effective results is a pressing challenge in the mental health field.[6] Owing to the 2019 coronavirus disease (COVID-19) pandemic, an increase in mental illnesses is expected that could persist for years. This suggests an even greater need to optimize resources for dealing with this major challenge.[7] A survey by the WHO[8] showed that the COVID-19 pandemic had suspended essential mental health services in about 93% of countries around the world while the population increasingly needs mental health care.

Clinical practice guidelines (CPGs) are fundamental to optimize these mental health resources, which will be in greater demand with the increased incidence of depression.[9] These guidelines contain recommendations for optimizing patient healthcare and have been developed through a review of the interventions and a cost-benefit analysis for each clinical health condition.[10] Hence, they enable the development of objective clinical decisions, help decrease clinical variability, educate patients and professionals on updated best practices, and improve the cost-effectiveness of healthcare.[11]

Among the interventions proposed in the CPGs, evidence-based pharmacotherapy is one of the strategies used to treat depression.[12] However, a previous study demonstrated a lack of information regarding the best approaches when pharmacological treatment for first-line depression fails.[13] Considering that the response to first-line treatment is only moderate (40%–60%) and remission after antidepressant treatment is achieved in only a minority of patients (30%–45%), there is a need to better investigate such gaps to improve the CPGs.[14]

Additionally, there is a lack of clarity in the guidelines on clinical actions, as well as a divergence among different guidelines about the sequence of strategies after inadequate or partial responses from depressed individuals.[13] Thus, to improve mental health professionals' clinical recommendations and provision of better healthcare to patients, in-depth evaluation of the guideline recommendations for patients who do not respond adequately to initial pharmacological interventions is necessary.

Study aims

This study aimed to assess similarities and differences in the recommended sequence of strategies among the most relevant guidelines for the pharmacological treatment of depression in adults who have shown an inadequate response to first-line treatment.

MATERIALS AND METHODS

A broad health search was conducted to explore the methodological quality and transparency of CPGs for the pharmacological treatment of non-communicable diseases, including depression. We updated the search of a previous Prospero systematic review (CRD42016043364)[15] and conducted an analysis specifically assessing CPGs that can be used by health professionals in primary and secondary (outpatient) care for the pharmacological treatment of depression in adults.

The second version of the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument was used to evaluate the quality of the CPGs identified in the research—a fundamental step of a systematic review. The recommendations of high-quality CPGs or those most commonly used in clinical practice[16] were compared to a method applied in a previous study published by the authors.[13]

Search data source

A comprehensive search was conducted on PubMed, Embase, and the Cochrane Library for CPGs published from January 1, 2011, to August 22, 2020 (Appendix 1). Twelve databases traditionally recognized as CPG repositories were also consulted.[13,17,18] Mendeley® software was used to conduct this search and remove duplicates.

Eligibility criteria

Only CPGs that made pharmacological recommendations for the treatment of depression in individuals aged 18 years or older were included. The following CPGs were excluded: those that did not have the full text available in Portuguese, English, or Spanish; those that focused on psychotherapeutic treatment or neuromodulation; and those for specific populations, such as patients with cancer, multiple sclerosis, or pregnant or lactating women. The latest versions of CPGs found on the original authors' websites were included. Two evaluators independently read the titles and abstracts of the retrieved articles, and—if the content met the eligibility criteria—the full text was evaluated. Discrepancies were resolved by one of the authors (GCHFM) who acted as the third evaluator. The latest version of each CPG, and all related complementary documents, were sent to the evaluators for a quality assessment using the AGREE II.

Extraction of general data and evaluation of CPG quality

Previously validated forms[18] were used by two independent reviewers for data extraction. A third reviewer resolved the discrepancies. The following data were extracted: type of

organization that produced the CPG (government organization or specialized society), country, method used to classify the evidence, and the CPG development method (whether done using adaptation methodology or other methods). Three independent researchers (FCG, IBS, and ST) evaluated the CPGs using the six AGREE II domains. The AGREE II contains 23 items grouped into six domains and two global classifications (general evaluation items). Each AGREE II domain evaluates a different dimension of CPG quality[19]: scope and purpose (domain 1), stakeholder involvement (domain 2), rigor of development (domain 3), clarity of presentation (domain 4), applicability (domain 5), and editorial independence (domain 6). A Likert scale ranging from 1 to 7 was used to evaluate the 23 items. Each reviewer entered an evaluation into the AGREE II platform for each item. The calculation was made automatically on the platform for each quality domain. Further, owing to the substantial heterogeneity of the general evaluation items, our protocol defined that these items would not be included in the analyses and that we would primarily focus on domain 3. All evaluators underwent rigorous training on the AGREE II application before making the quality assessment (details of this training have been previously published[18]). Discrepancies of two or more points were discussed by the evaluators until consensus was reached. The score was calculated individually for each domain.

Comparison of recommendations

The recommendations of high-quality CPGs, defined as those with a score of 80% or above in domain 3 of AGREE II and those known to be most commonly used in clinical practice,[16] as well as the ones developed by an important CPG developer institution, were compared. Domain 3 (methodological rigor) was used to classify a CPG as "high-quality" since this is the most important item regarding the reliability of the recommendations.[20] Two independent researchers extracted all recommendations from the selected CPGs.

This included extracting the quality of the evidence and the strength of the recommendation. Recommendations for patients who did not respond to the first-line pharmacological treatment were grouped as follows: patient reevaluation, dosing adjustment, switching, combination, and medication augmentation.

Patient and Public Involvement

No patient involved

RESULTS

We identified 1951 records in Medline (n = 691), Cochrane (n = 105), and Embase (n = 1155), and 44 additional records through the other 12 specific websites for CPGs. After removing 165 duplicates using Mendeley®, 1830 documents remained. Subsequently, by reading the full text and applying the eligibility criteria, we selected eight CPGs for this study (Figure 1). Appendix 2 includes the reasons for excluding documents. We identified five CPGs that presented a score ≥ 80% for domain 3 in AGREE II; thus, they were considered high-quality guidelines. In addition to these selected CPGs, two more were included based on their widespread acceptance[16]: guidelines of The Canadian Network for Mood and Anxiety Treatments (CANMAT)[21] and the American Psychiatric Association.[22] Further, the guideline for the Management of Major Depressive Disorder developed by the Department of Veterans Affairs (VA), in collaboration with the Department of Defense (DoD), was also included as it was scored very close to the cutoff point. Additionally, the VA/DoD has been identified by the National Academy of Medicine as a leader in clinical practice guideline development.[23] The eight CPGs that were regarded as high quality and had been selected were: *Guía Clínica* AUGE (score = 89%)[24]; *Guía de Práctica Clínica* (score = 86%)[25]; Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Depression in Adults: Recognition and Management (score = 84%)[26]; Depression, Adults in Primary Care (score = 81%)[27];

Practice Guidelines for the Treatment of Patients with Major Depressive Disorder (score = 46%)[22]; CANMAT (score = 54%)[21]; Clinical Practice Guideline for the Treatment of Depression across Three Age Cohorts (score = 81%)[28]; and VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder (score = 78%).[23] Table 1 briefly describes the characteristics of all the CPGs.

Terminology in guidelines and the description of treatment sequences

Less than half of the guidelines (*n* = 3, 37%) clearly defined responsiveness to treatment; that is, these guidelines defined who was a partially responsive or unresponsive patient.[21,23,27] Only two of these guidelines that included a definition of responsiveness also described a clear sequence to be adopted in clinical practice for the management of these patients.[21,27] Additionally, only half of the guidelines (*n* = 4) clearly defined refractory or resistant depression[23-25,27] and only two of these provided a sequential and clear form for the specific patient population.[24,27] Only the VA/DoD guidelines offered recommendations for both resistant depression and patients who were partially responsive to treatment.[23] Tables 2 and 3 present a detailed description of the definitions proposed by the guidelines concerning adequate and inadequate response to first-line treatment, the presence and sequence of strategies to be implemented in case of inadequate response or resistant depression, and as other considerations outlined by the guidelines.

Treatment recommendations for patients nonresponsive to first-line pharmacological treatment for depression

Two guidelines specified the wait time required before increasing the treatment dosage (Table 4). Additionally, five guidelines reported the wait time before reassessing antidepressant effectiveness and declaring the patient nonresponsive: 3 weeks,[25] 2–4 weeks,[26] 6 weeks,[23] and 4–8 weeks.[22,28]

Most guidelines agree on verifying treatment adherence before considering whether a patient is responsive or not to the first line of standardization.[21-25] Additionally, most also mention the importance of reassessing the diagnosis, and some specify bipolar disorder in this context (Table 4). Some guidelines have mentioned such divergences, including differences among the guidelines regarding the therapeutic alternatives recommended for nonresponsive patients. It is noteworthy that one of the guidelines indicated the substitution of pharmacotherapy with psychotherapy.[23] However, most guidelines indicated that these alternatives should include medication changes, such as dosage adjustment, substitution of medications, combination of medications, and augmentation of medications. Most (87%) guidelines[21,22,24-28] indicated that an increase in drug dosage should be considered a valid therapeutic alternative for patients who did not respond to treatment. The APA guideline[22] effectively detailed alternatives for augmentation medications for nonresponsive patients, suggesting lithium, anti-psychotics, and thyroid hormones, which were also indicated in the Colombian guideline.[25] It was only the NICE[26] and CAMNAT[21] guidelines that clearly specified the time that should elapse before increasing the dosage; however, these durations differed (CANMAT: 2–4 weeks and NICE: 3–4 weeks). Thus, although most CPGs emphasized the importance of adjusting medication dosages in cases where patients do not respond to first-line treatment, they did not specify the wait time duration. Moreover, almost all, except for the VA/DoD guideline,[23] explicitly mentioned switching antidepressants in these cases. Regarding the adverse events that may occur when trying pharmacological therapeutic alternatives, the APA guideline made it very clear that, in these cases, it is possible to consider replacing the drug or treating the adverse event.[22]

DISCUSSION

Although there are many modalities for treating depression, pharmacotherapy remains the most common first-line strategy.[12] However, symptom remission after pharmacological treatment with first-line antidepressants was only achieved in a minority of patients.[14,67] Thus, this study aimed to assess the similarities and differences in the recommended sequence of strategies, among the most relevant CPGs, for the pharmacological treatment of depression in adults who have shown an inadequate response to first-line treatment.

Relevant findings regarding such recommendations included: (1) the guidelines did not present a standardized definition of an adequate response, and (2) they exhibited differences related to the time that must elapse before declaring that a patient did not respond adequately to initial treatment.

Alternately, the guidelines agreed on the importance of checking adherence before considering an adequate response to pharmacotherapy and on the indications for a gradual increase in the dosage of drugs. However, most guidelines lacked information about the expected time that should elapse before increasing the dosage in clinical practice. Consequently, variations in clinical practice may also be relevant. In contrast with the others, one guideline mentioned the substitution of drugs for psychotherapy in patients who did not respond to initial pharmacological therapy.

The standardized definition of an adequate response—one that is satisfactory to the given treatment—was not always clear. This is a critical point—considering that we are dealing with high-quality guidelines—which possibly represents the highest level of evidence to guide clinical decision-making.[12] The absence of a clear definition of an adequate response restrains the applicability of the recommendations for patients who do not respond to initial pharmacological interventions.

Considering the lack of consensus in the literature about what constitutes an adequate response, a clear definition of an adequate response to treatment is fundamental to guide the step-by-step process presented in the clinical guidelines for patients who do not display an adequate response (e.g., resistant depression).[68] Notably, the longer a patient's depression lasts—that is, the lower the response to pharmacological treatment (be it a first- or second-line strategy)—the higher the chance of a more severe course of the disorder and, potentially, suicide.[69] Therefore, filling the literature gap and defining adequate response, nonresponse, and partial response to depression treatment are crucial for clinical guidelines to help advance the treatment of these patients.

Discrepancies in recommendations for patients who did not respond to first-line treatment were also observed by MacQueen et al.[12] The researchers analyzed 21 CPGs published between 1980 and 2015 and used in primary care for the treatment of major depression, dysthymia, and minor depression with the AGREE II instrument. Concerning first-line treatment, MacQueen et al.[12] found discrepancies related to the recommended dosage, alternative treatments, and duration of treatment before making therapeutic changes. We have also confirmed their findings regarding the lack of a definition for inadequate response to treatment in the guidelines.[12]

Notably, more clinical trials are needed for this specific population. This could contribute to consistency in the recommendations of future guidelines. Health professionals are hesitant to use CPGs in clinical practice because of the discrepancies.[70] Thus, to minimize discrepancies, the quality of the guidelines must be improved so that healthcare professionals find them more reliable and implement the recommendations.[71] A change in the attitude of these professionals is key to the implementation of CPGs[72] and to the achievement of optimal patient care.

This study was limited in that it only included papers written in English, Portuguese, or Spanish. However, most guidelines are published in these languages. Moreover, since the AGREE II is an assessment method, there is some inherent subjectivity in the use of an instrument to assess quality. Hence, to minimize this, the appraisers discussed any discrepancies in their notes for each item until consensus was achieved. Another limitation was that the recommendations might not have been identified as main recommendations because they are often spread throughout the text of the guidelines. This often occurs when the guideline discusses the evidence but does not make a clear recommendation, thus creating doubt about whether it is a recommendation.

Despite these limitations, this study had several strengths. Among these was the inclusion of two guidelines[21,22] that are often used in clinical practice in addition to those with the highest score in domain 3 of the AGREE II. Such a strategy enabled a broader discussion of clinical questions mentioned in the CPGs. Other strengths of this study included the comprehensive search of the literature and the careful training of our appraisers. In describing the recommendations in the tables, we have offered a comparative view of distinct CPGs, which provides physicians and patients with a more comprehensive understanding of pharmacological approaches to the treatment of depression. Our findings can aid in the elaboration or adaptation of a CPG, as we identified important divergences between CPGs to which patients and professionals should pay special attention. The step-by-step process of pharmacological management of adult patients who do not respond to first-line pharmacological treatment of depression needs to be clarified in the guidelines. Currently, while there is little evidence in the literature on this specific recommendation, this can be helpful in leading to an improvement in patient-related outcomes. Moreover, identification of the points on which CPGs converge fully and that have been well-addressed in certain CPGs may also be

helpful for the elaboration or adaptation of a CPG for local contexts, as well as for contributing to clinical decisions regarding treatment for depression. Considering that healthcare professionals have little available time to read literature in their field and that the amount of information available has grown exponentially,[73,74] there is a need to base decision-making on evidence synthesis that is reliable.

In conclusion, the guidelines most often referenced for the pharmacological treatment of depression differed in recommendations for nonresponsive patients, mainly in their recommended sequence of strategies. The definition of partial or adequate response to treatment, as well as that of symptomatic remission, must be clarified and standardized in future guidelines to effectively improve patient care.

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Contributors

FCG, DOM, and ATS planned and developed the literature search strategy. IBS conducted the literature search. FCG and GCHFM realized the literature review. FCG, DOM, ATS, RF, ER, and IBS planned and developed the methodology. FCG, DOM, ATS, and ER conducted the data analysis. FCG, DOM, ATS, and ER interpreted the data. FCG, DOM, GCHFM, ATS, AFO, RF, ER, and IBS wrote the draft and final version of the article. DOM, ATS, AFO, RF, ER, and IBS reviewed the article. FCG and IBS appraised the guidelines. All authors approved the final article.

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Competing interests

None declared.

Patient consent for publication

Not required.

Data availability statement

The data supporting the study findings are openly available.

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Table 1. Characteristics of clinical practice guidelines and Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II) domain scores (%)

Clinical practice guideline (year)	D 1	D 2	D 3	D 4	D 5	D 6	Organization type	Country or region	Evidence classification mode	Method for guideline development
Depresión en personas de 15 años y más (Ministerio de Salud) (CHL),2013.	83	76	89	94	57	17	Governmental organization	Chile	GRADE modified	New development
Detección temprana y diagnóstico del episodio depresivo y trastorno depresivo recurrente en adultos. Atención integral de los adultos con diagnóstico de episodio depresivo o trastorno depresivo recurrente (Ministerio de Salud (COL), 2015)	100	85	86	100	96	92	Governmental organization	Colombia	GRADE	Adapted
Depression in adults: Recognition and management (National Institute for Health and Care Excellence [NICE], 2009)	89	83	84	81	71	75	Governmental organization	England	GRADE	New development
Institute for Clinical Systems Improvement Health Care Guideline: Depression, Adults in Primary Care (Trangle et al., 2016)	96	78	81	91	72	97	Consortium	United States	GRADE	New development
Clinical practice guideline for the treatment of depression across three age cohorts. 2019 (American Psychological Association, 2019)	91	67	81	80	57	83	Specialty society	United States	GRADE	New development
VA/DoD clinical practice guideline for the management of the major depressive disorder (The Management of Major Depressive Disorder Working Group, 2016)	93	76	78	94	38	58	Specialty society	United States	GRADE	New development
Diagnosis and treatment of depression in adults: 2012 clinical practice guideline (Kaiser	83	63	76	93	46	58	Specialty society	United States	GRADE	Adapted

Permanente Care Management Institute, 2012).										
Clinical practice guideline on the management of depression in adults (Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, Ministry of Health, Social Services and Equality, 2014).	94	93	70	91	57	53	Governmental organization	Spain	Own method	New development
Delirium, dementia, and depression in older adults: Assessment and care (Registered Nurses' Association of Ontario, 2016).	72	74	69	80	76	86	Specialty society	Canada	Own method	New development
Guía de Práctica Clínica para el Tratamiento de la Depresión en Atención Primaria (García-Herrera et al., 2011).	70	44	69	80	50	69	Governmental organization	Spain	GRADE	New development
Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. (Qaseem et al., 2016)	80	39	69	70	32	67	Specialty society	United States	GRADE	New development
Diagnóstico y Tratamiento de la Depresión en el Adulto Mayor en el Primer Nivel de Atención (Instituto Mexicano del Seguro Social, 2011).	87	46	69	83	14	67	Governmental organization	Mexico	Own method	Adapted
IMSS-161-09, Diagnóstico y tratamiento del trastorno depresivo en el adulto. 2015. (Secretaría del Salud, 2015)	81	43	69	80	32	31	Governmental organization	Mexico	Graduation scale of the CPG	Adapted
Intervenciones de enfermería para la detección, atención y control de la depresión en el adulto mayor en los tres niveles de atención. (Secretaría del Salud, 2016).	94	56	63	81	42	64	Governmental organization	Mexico	Graduation scale of the CPG included in the adaptation by Shekelle, 2018	New development
Ministry of Health clinical practice guidelines: depression (Chua et al., 2012).	78	72	60	89	50	28	Governmental organization	Singapore	Own method	Adapted

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (Malhi et al., 2015)	74	63	58	78	24	67	Governmental organization	Australia	Does not mention	New development
Management of first depression or generalized anxiety disorder episode in adults in primary care: A systematic metareview (Driot et al., 2017)	69	30	56	72	11	83	Independent authors	France	Does not mention	New development
World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders (Bauer et al., 2013).	61	54	54	83	32	75	Governmental organization	Several countries	Own method	New development
Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments (Kennedy et al., 2016)	63	48	54	89	26	53	Specialty society	Canada	Own method	New development
Evidence-based guidelines for mental, neurological, and substance use disorders in low- and middle-income countries: summary of WHO recommendations (Dua et al., 2011).	69	74	50	74	29	75	Governmental organization	Several countries	GRADE	New development
Florida best practice psychotherapeutic medication guidelines for adults with major depressive disorder (McIntyre et al., 2017)	87	56	48	83	32	69	Specialty society	United States	Own method	New development
World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 2: Maintenance (Bauer et al., 2015)	69	48	47	61	28	75	Specialty society	Associations of several countries	Own method	New development
Management of major depressive disorder (2nd ed.) (Malaysian Health Technology Assessment Section, 2019)	81	50	47	70	54	78	Governmental organization	Malaysia	SIGN adapted	New development
Practice guideline for the treatment of patients with major depressive disorder. Gelenberg et al., 2010)	48	43	46	83	44	42	Specialty society	United States	Own method	New development

Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines (Cleare et al., 2015)	67	57	40	69	13	58	Specialty society	England	Own method	New development
Pharmacological treatments for patients with treatment-resistant depression (Ruberto et al., 2020)	43	11	35	39	1	72	Independent authors	United States	Does not mention	New development
Major depressive disorder in adults: Diagnosis & Management (Guidelines and Protocols Advisory Committee, Ministry of Health, British Columbia, 2013)	85	37	35	85	39	42	Governmental organization	Canada	Own method	New development
The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on unipolar nonpsychotic depression (Giakoumatos and Osser, 2019)	61	19	33	83	26	75	Specialty society	United States	Does not mention	New development
Pharmacological treatment of unipolar depressive disorders: summary of WFSBP guidelines (Bauer et al., 2017)	56	41	23	76	21	50	Specialty society	Associations of several countries	Own method	New development
Clinical guidelines for the management of treatment-resistant depression: French recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental (Bennabi et al., 2019)	50	33	22	65	13	67	Specialty society	France	Does not mention	New development
The South African Society of Psychiatrists (SASOP) Treatment Guidelines for Psychiatric Disorders (Grobler, 2013).	50	48	19	67	13	19	Specialty society	South Africa	Does not mention	New development
If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies (Connolly and Thase, 2011).	63	17	17	52	13	72	Independent authors	United States	Does not mention	New development
Korean medication algorithm for depressive disorder: comparisons with other treatment guidelines (Wang et al., 2014).	56	13	17	43	6	58	Specialty society	Korea	Does not mention	New development

Depression in the primary care setting (Park and Zarate, 2019)	33	22	17	50	18	31	Independent authors	United States	Does not mention	New development
Management of treatment-resistant depression: Challenges and strategies (Voineskos et al., 2020)	44	11	15	50	10	22	Independent authors	Canada	Does not mention	New development
Evidence-based practice guideline for the treatment of adult patients with depressive disorders. Part I: Psychiatric management (Voytenko et al., 2018)	54	39	15	65	8	42	Independent authors	United States	Does not mention	New development
Guidelines of the Polish psychiatric association – Wroclaw division, the Polish Society of Family Medicine and the College of Family Physicians in Poland for diagnosis and treatment of depressive disorders in primary health care (Piotrowski et al., 2017)	54	26	15	72	25	50	Specialty society	Poland	Does not mention	New development
How to choose an antidepressant medication (Bayes and Parker, 2019)	46	22	14	48	07	33	Independent authors	Australia	Does not mention	New development
Pharmacological management of unipolar depression (Malhi et al., 2013).	44	20	13	63	17	39	Governmental organization	Australia	Does not mention	New development
A systematic approach to pharmacotherapy for geriatric major depression (Mulsant et al., 2014).	50	28	13	61	08	36	Governmental organization	Canada	Does not mention	New development
Clinical practice guidelines for management of depression in the elderly (Avasthi and Grover, 2018)	70	24	12	80	36	0	Independent authors	India	Does not mention	New development
Position statement of the European Psychiatric Association on the value of antidepressants in the treatment of unipolar depression (Möller et al., 2012).	28	15	12	11	10	33	Governmental organization	Several countries	Does not mention	New development
Combined treatment of depression (Busch and Sandberg, 2012).	46	11	10	65	15	17	Independent authors	United States	Does not mention	New development
Clinical Practice. Depression in the elderly (Taylor, 2014)	41	7	8	57	8	33	Independent authors	United States	Does not mention	New development

Diagnostic and therapeutic protocol of depression (Sanchez and Santos, 2019)	54	24	6	61	8	33	Independent authors	Spanish	Does not mention	New development
Clinical practice guidelines for the management of depression (Gautam et al., 2017).	39	20	6	57	15	0	Independent authors	India	Does not mention	New development

Note. GRADE: Grades of Recommendation Assessment, Development and Evaluation; CHL: Chile; COL: Colombia; VA/DoD: United States Department of Veterans Affairs/Department of Defense; WFSBP: World Federation of Societies of Biological Psychiatry; WHO: World Health Organization; CPG: Clinical Practice Guidelines

Table 2. Guideline definitions of adequate/inadequate response to first-line treatment and strategies for patients who respond inadequately

Guideline	Terminology for patients who do not show an adequate response to first-line treatment	Definition of inadequate response to first-line treatment (if it is defined)	Guideline establishes sequence of therapeutic strategies for this population	Reevaluation	Increase consultation frequency	Adjusting dosage	Switching	Combination	Augmentation	Combining pharmacotherapy with psychological treatments	Substitution of drugs with non-pharmacological therapy	Other considerations
Depresión en personas de 15 años y más. 2017. (Ministerio de Salud [CHL], 2013)		Not defined										
Detección temprana y diagnóstico del episodio depresivo y trastorno depresivo recurrente en adultos. Atención integral de los adultos con diagnóstico de episodio depresivo o trastorno depresiv		Not defined										

o recurrente (Ministerio de Salud [COL], 2015												
Depression in adults: Recognition and management (NICE, 2009)	Patient with inadequate response	Defined	Yes, proposes a step-by-step care plan for these patients, although the sequence is not clear owing to its form of presentation	Yes, check adherence and side effects (first strategy)	Yes, second	Yes, (third)	Yes (fourth)	Yes (fifth)	Yes (fifth too)	Yes (sixth)		Augmentation for the NICE guideline is augmenting antidepressants with classes of drugs other than antidepressants.
ICSI Health Care Guideline: Depression, Adults in Primary Care (Trangle et al., 2016)		Not defined										
Clinical practice guideline for the treatment of depression across three age cohorts. (APA, 2019)	Partially- or non-responsive to initial antidepressant treatment	Not defined	Does not mention a sequence clearly. Substitution of drugs by non-pharmacological therapy, switching antidepressants, combination of antidepressants with non-pharmacological therapy or augment				Yes		Yes		Yes	Unlike NICE, it uses augmentation to mean augmenting antidepressants with antidepressants For non-responders or partial responders to second generation pharmacological therapy, no

			ation of antidepressants with other drugs are mentioned alternatives							evidence for preference between switching to another second generation antidepressant, changing to non-pharmacology (self-help cognitive therapy), or augmentation treatment with guided self-help,
VA/DoD clinical practice guideline for the management of major depressive disorder (The Management of Major Depressive Disorder Working Group, 2016)	Partial response defined as less than 50% reduction of symptoms	Very clear definition for partial response	Does not state the sequence very clearly	Yes	Yes	Yes	Yes	Yes	Yes	
Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of	Patient with partial or no response (both referred to as an "inadequate response")	Defined	Sequence of strategies not explicitly stated despite, having used an algorithm for patients with inadequate	Yes			Yes	Yes		An adjunct strategy (the addition of a second medication to an initial medication) is the preferred term over

adults with major depressive disorder: Section 3. Pharmacological Treatments (Kennedy et al., 2016)	**Partial response:** Reduction of scores by 25-49%. **No response:** Less than 25% reduction in scores		response to antidepressants The algorithm indicates the importance of considering factors when switching antidepressants or using adjuvant therapy" ?								combination (adding a second antidepressant to the first) or augmentation (adding another medication that is not an antidepressant). Psychotherapy or neuro-stimulation may be considered for a patient with an inadequate response to the initial antidepressant.
Practice guideline for the treatment of patients with major depressive disorder (Gelenberg et al., 2010)	"Adequacy of treatment response" defined. A figure indicates the strategies that must be followed both for nonresponsive and for partially responsive patients at each stage of treatment, including weekly	Unclear definition regarding the percentages of changes in the scales to measure depression.	Presented in a sequential form in the figure but throughout the text it is presented otherwise In the figure (for nonresponsive and partially responsive patients): **Initial weeks:** Assess adherence. If treatment is well tolerated, consider increasin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Patients with a history of poor adherence to treatment or incomplete response to adequate trials of single treatment modalities can benefit from combined treatment with medication and psychotherapy focused on depression.

	arrangements	g the dosage of the medication or the intensity of psychotherapy, especially if there is no response. If symptoms are severe or life-threatening, consider ECT. **4-8 weeks of treatment:** In patients treated with an antidepressant, consider increasing the dose (if well tolerated), changing to a different antidepressant, switching to or augmenting with psychotherapy, using potentiation therapy or ECT. For an insufficient response to psychotherapy, change the intensity or type of

	psychotherapy or add/substitute with medication.
	Throughout the treatment: In case of significant antidepressant side effects, consider switching to a different antidepressant, reduce the dose, or treat the side effect, or switch to psychotherapy or ECT. If the trials of two drugs in the same class of antidepressants were ineffective, consider moving antidepressants to a different class. For patients who have difficulty tolerating psychotherapy, consider changing the intensity or type of therapy

	or adding or changing medication.

Note. CHL: Chile; COL: Colombia; NICE: National Institute for Health and Care Excellence; ICSI: Institute for Clinical Systems Improvement; APA: American Psychiatry Association; VA/DoD: United States Department of Veterans Affairs/Department of Defense; ECT: Electroconvulsive therapy

Table 3: Guideline definitions refractory/ resistant and strategies for patients

Guideline	Terminology for patients who do not show refractory/resistant depression	Definition of the term (if it is defined)	Sequence of therapeutic strategies established for this population	Reevaluation	Increase consultation frequency	Adjusting dosage	Switching	Combination	Augmentation	Combining pharmacotherapy with psychological treatments	Substitution of drugs with non-pharmacological therapy	Other considerations
Depresión en personas de 15 años y más. 2017. (Ministerio de Salud [CHL], 2013)	Refractory depression "depresión resistente o refractaria" Seems to have considered the two terms distinct	**Resistant depression**: one that does not respond to adequate treatment, at the appropriate dose, for the appropriate time. Also defined as depression that presents an invalid or poor response to one or more therapeutic	Yes, establishes sequence for refractory depression interventions .	Yes (first strategy)		Yes (second strategy)	Yes (third strategy)	Yes (Fifth strategy)	Yes (Fourth strategy			Mentions: Mindfulness, cognitive behavioral therapy, psychoeducation (resistant depression). For resistant severe depression, modi

		treatments administered in adequate doses, methods, and times.								fied electroconvulsive therapy is recommended.
		As for refractory depression, it only mentions biological interventions without defining them. It is not clear whether it was considered synonymous. The the interventions recommended are valid for both refractory and resistant depression, although with a different sequence for each.	For refractory depression, a sequence is understood	Yes (first strategy)	Yes (second strategy)	Yes (fourth strategy)	Yes (Fifth strategy)	Yes (third strategy)		
Detección temprana y diagnóstico del	Refractory or resistant depression	Treatment resistance defined as the absence	Sequence of interventions not specified;	Yes	Yes	Yes	Yes	Yes	Yes	Neuro-stimulation, electrocon

episodio depresivo y trastorno depresivo recurrente en adultos. Atención integral de los adultos con diagnóstico de episodio depresivo o trastorno depresivo recurrente ((Ministerio de Salud [COL], 2015)	considered as being synonyms “depresión refractaria o resistente”	of sustained remission, with respect to severity of depressive symptoms or alteration of functionality, even after appropriate treatment both in terms of duration and dose.	only mentions optimizing the dose and reassessing diagnosis; adherence and adverse events must be considered before the addition of psychotherapy, substitution of combination medications, and augmentation of medications			vulsive therapy, and transcranial magnetic stimulation are valid therapeutic options for these patients.
Depression in adults: Recognition and management (NICE, 2009)	Does not use the refractory or resistant depression nomenclature					

ICSI Health Care Guideline: Depression, Adults in Primary Care (Trangle et al., 2016)	Depression-resistant patient defined **Partial positive response to medication**: at least 25% reduction in symptoms after 6 weeks with a therapeutic dose	Clearly defines failure to achieve adequate trial remission (correct dose) through three antidepressants of different classes (stresses that its focus is primary care)	A very detailed step-by-step procedure mentioned	Yes (First and sixth strategy before augmentation-in case of bipolar, comorbidities, and substance abuse	Yes (Second)	Yes (Third)	Yes (Fifth and seventh) augmenting lithium and antipsychotic drugs)	Yes (Fifth)	Yes (Fourth)	Other strategies: phototherapy, electroconvulsive therapy, and hospitalization. Refer the patient to a mental health specialist if using MAOI
Clinical practice guideline for the treatment of depression across three age cohorts. (APA, 2019)	Does not use the refractory or resistant depression nomenclature									
VA/DoD clinical practice guideli	= Treatment resistance define	Resistant depression defined well	Sequence of strategies not explicitly							

ne for the manag ement of major depress ive disorde r (The Manag ement of Major Depres sive Disord er Workin g Group, 2016)	d as a lack of full respon se, despit e at least two adequ ate treatm ent trials.	stated. For patien ts with resista nt depres sion, it is recom mende d to offer MAOI s and TCAs in conju nction with patien t educat ion on safety and side effect. Also a possib ility to offer them transc ranial magne tic stimul ation
Canadi an Networ k for Mood and Anxiet y Treatm ents (CAN MAT) 2016 clinical guideli nes for	Does not use the refract ory or resista nt depres sion nome nclatu re	

the management of adults with major depressive disorder: Section 3. Pharmacological Treatments (Kennedy et al., 2016)	
Practice guideline for the treatment of patients with major depressive disorder (Gelenberg et al., 2010)	Does not use the refractory or resistant depression nomenclature

Note. CHL: Chile; COL: Colombia; NICE: National Institute for Health and Care Excellence; ICSI: Institute for Clinical Systems Improvement; APA:, American Psychiatry Association; VA/DoD: United States Department of Veterans Affairs/Department of Defense; MAOI: Monoamine Oxidase Inhibitor; TCA: Tricyclic Antidepressants

Table 4. Clinical practice guidelines for the pharmacological treatment of depression: patients with partial or no response

Recommendations/clinical practice guidelines	Depresión en personas de 15 años y más. 2017. (Ministerio de Salud [CHL], 2013),	Detección temprana y diagnóstico del episodio depresivo y trastorno depresivo recurrente en adultos. Atención integral de los adultos con diagnóstico de episodio depresivo o trastorno depresivo recurrente (Ministerio de Salud [COL], 2015)	Depression in adults: Recognition and management (NICE, 2009)	ICSI Health Care Guideline: Depression, Adults in Primary Care (Trangle et al., 2016)	VA/DoD clinical practice guideline for the management of major depressive disorder (The Management of Major Depressive Disorder Working Group, 2016)	Clinical practice guideline for the treatment of depression across three age cohorts. (APA, 2019)	CANMAT 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments (Kennedy et al., 2016)	Practice guideline for the treatment of patients with major depressive disorder (Gelenberg et al., 2010)
Clear presence of a definition								
• Partially responsive patient	-	-	-	✓	✓	-	✓	-

• Nonresponsive patient	-	-	-	-	-	-	✓	-
• Inadequate response or adequacy of treatment response undefined, but step-by-step care for patients mentioned	-	-	-	-	-	-	-	✓
• Inadequate response to treatment undefined, but sequential recommendations for resistant or refractory depression provided	✓	-	-	✓	-	-	-	-
• Inadequate response to treatment undefined; recommendations for refractory or resistant depression provided, although not sequentially	-	✓	-	-	-	-	-	-
• Refractory or resistant depression defined	✓	✓	-	✓	✓	-	-	-
• Does not define treatment for partially responsive patients and does not have a clear sequence for these patients	-	-	-	-	-	✓	-	-

• Partial response defined, but does not have a clear sequence for the treatment of patients	-	-	-	-	✓	-	✓	-
Clear description of waiting period prior to declaring that the patient had a partial, inadequate, or no response to the initial pharmacological treatment	-	✓	✓	-	✓	✓	✓	-
• Duration of waiting period prior to declaring that the patient had a partial, inadequate, or no response to the initial pharmacological treatment	-	3 weeks	4 weeks	6 weeks	4–6 weeks	4–8 weeks	2–4 weeks	4–8 weeks
Clear description of waiting period before changing the dose of antidepressants	-	-	✓	-	-	-	✓	-
• Duration of waiting period before changing the dose of antidepressants	-	-	3–4 weeks	-	-	-	2–4 weeks	-

A clear and organized sequence established for treating patients with an inadequate response	✓	-	-	✓	-	-	-	-
No clear sequence established for treating patients with an inadequate response; however, it is possible to assume a sequence in the order of the recommendations	-	✓	✓	-	✓	✓	✓	-
Recommendations in case of patients with an inadequate response								
• Reassess the diagnosis	✓	✓	-	-	✓	-	✓	✓
• Suspect bipolar disorder	✓	✓	-	-	-	-	-	-
• Check for the presence of comorbidities	✓	-	-	-	✓	-	✓	✓
• Check for psychosocial factors that predict poor response to	-	-	-	-	-	-	-	✓

pharmacological treatment								
• Check for the presence of a personality disorder	✓	✓	-	-	-	-	-	-
• Check for the presence of a substance-use disorder	-	✓	-	✓	-	-	✓	-
• Check adherence to pharmacological treatment	-	✓	✓	✓	-	-	✓	✓
• Check to ensure if the treatment time was adequate before declaring that the patient is not responding or with an inadequate response	-	-	-	-	-	-	-	✓
• Check the quality of the therapeutic alliance	-	-	-	-	-	-	-	✓
• Check for any side effects	-	✓	✓	✓	-	-	-	✓

• Increase the frequency of consultations and monitor the results	-	-	✓	-	-	-	-	-
• Reintroduce previous treatments administered incorrectly (for example, at an inadequate dose)	-	-	✓	-	-	-	-	-
• Switching from antidepressants to non-pharmacological therapy as a possibility	-	-	-	-	✓	✓	-	✓
Therapeutic options (interventions for patients with a partial, inadequate, or no response to the initial pharmacological treatment)								
• Dosage adjustment	✓	✓	✓	✓	-	✓	✓	✓
• Switching antidepressants	✓	✓	✓	✓	-	✓	✓	✓
• Combination or augmentation drugs	✓	✓	✓	✓	-	✓	✓	✓

• Addition of psychotherapy (combination of treatments)	-	-	✓	✓	✓	✓	-	✓
• Substitution of drugs by non-pharmacological therapy	-	-	-	-	✓	-	-	-
Switching antidepressants (drug classes)	-	✓	✓	✓	✓	✓	✓	-
• Switching serotonin selective reuptake inhibitors with serotonin-norepinephrine reuptake inhibitor	-	-	-	-	-	✓	-	-
• Switching with monoamine oxidase inhibitor (as a possibility)	-	✓	-	✓	✓	✓	✓	-
First among the same class (serotonin selective reuptake inhibitors), then different classes (tricyclic antidepressants,	-	-	✓	-	-	-	-	-

monoamine oxidase inhibitor)								
• witching antidepressants with tricyclic antidepressants	-	✓	✓	-	-	-	✓	-
Criteria established to decide between either replacing the antidepressant or augmenting it with another medication / another antidepressant	-	✓	-	-	✓	-	✓	-
Criteria established for suggesting psychotherapy for patients with an inadequate first-line treatment response or the combination of psychotherapy and pharmacotherapy	-	-	-	-	-	-	-	-
Guideline suggests adding psychotherapy to drugs as a possibility for the treatment of non-responders	-	✓	✓	✓	✓	✓	-	✓
The specific types of psychotherapy recommended for patients with an inadequate response to first-line pharmacological treatment	-	-	Cognitive behavioral therapy, cognitive behavioral therapy in	Cognitive psychotherapy in combination with drugs	Cognitive behavioral therapy, interpersonal therapy, psychodynamic therapy	-	-	-

			combination with drugs					
Therapeutic strategies, based on the primary or other concomitant pathology of patients, indicated for those with inadequate response to first-line pharmacological treatment	✓	✓	-	-	-	-	-	-

Note. CHL: Chile; COL: Colombia; NICE: National Institute for Health and Care Excellence; ICSI: Institute for Clinical Systems Improvement; APA:, American Psychiatry Association; VA/DoD: United States Department of Veterans Affairs/Department of Defense; CANMAT, Canadian Network for Mood and Anxiet

Figure 1. Flowchart of clinical practice guidelines selection.

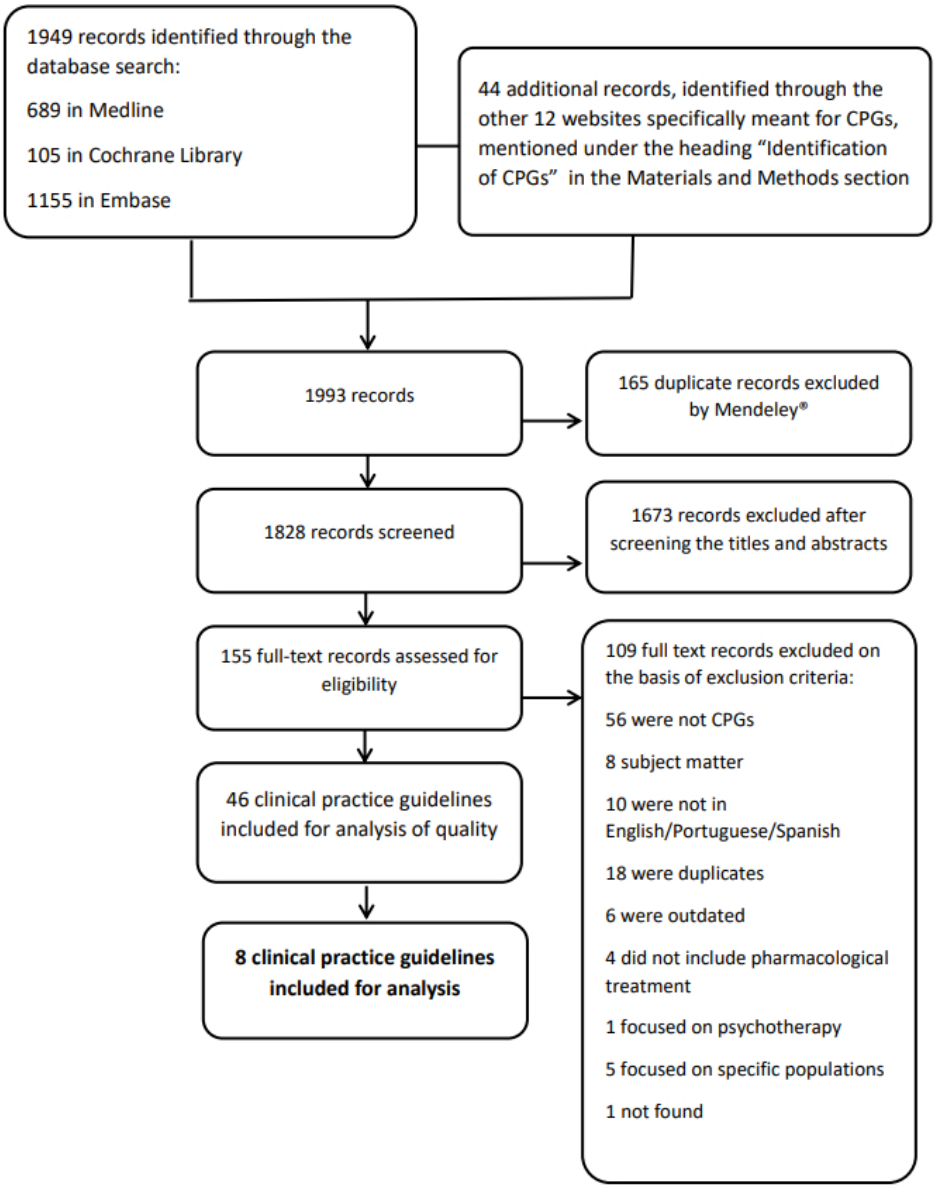

Figure 1. Flowchart of clinical practice guidelines selection.

118x150mm (144 x 144 DPI)

Appendix 1. Systematic search strategies

Medline (PubMed website)

(((((("Guideline" [Publication Type] OR "Guidelines as Topic"[Mesh] OR "Practice Guideline" [Publication Type] OR "Health Planning Guidelines"[Mesh]) OR "Clinical Protocols"[Mesh])) OR ("Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus"[Mesh]))) OR "Standard of Care"[Mesh])) "Guideline" [Publication Type] OR "Guidelines as Topic"[Mesh] OR "Practice Guideline" [Publication Type] OR "Health Planning Guidelines"[Mesh]) OR "Clinical Protocols"[Mesh])) OR ("Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus"[Mesh]))) OR "Standard of Care"[Mesh])))))) AND (("Depressive Disorder"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR Depressive Disorders OR Disorder, Depressive OR Disorders, Depressive OR Neurosis, Depressive OR Depressive Neuroses OR Depressive Neurosis OR Neuroses, Depressive OR Depression, Endogenous OR Depressions, Endogenous OR Endogenous Depression OR Endogenous Depressions OR Depressive Syndrome

OR Depressive Syndromes OR Syndrome, Depressive OR Syndromes, Depressive OR Depression, Neurotic OR Depressions, Neurotic OR Neurotic Depression OR Neurotic Depressions OR Melancholia OR Melancholias OR Unipolar Depression OR Depression, Unipolar OR Depressions, Unipolar OR Unipolar Depressions))

Cochrane Library

1—MeSH descriptor: [Guideline] explode all trees

1—MeSH descriptor: [Consensus] explode all trees

1—MeSH descriptor: [Clinical Protocols] explode all trees

1—#1 OR #2 OR #3

1—MeSH descriptor: [Depression] explode all trees

EMBASE

#1 'practice guideline'/mj OR 'consensus development'/exp/mj OR 'clinical protocol'/mj
#2 'depression'/exp
#3 #1 AND #2

Appendix 2. Reasons for excluding clinical practice guidelines

References of the excluded guidelines	Reasons for exclusion
Institute for Clinical Systems Improvement. *Adult Depression in Primary Care*. Bloomington, MN: ICSI; 2016.	Duplicate
Austin M-P, Highet N, The Expert Working Group. *Mental Health Care in the Perinatal Period: Australian Clinical*	Duplicate

Practice Guideline. Melbourne, Australia: Centre of Perinatal Excellence; 2017.	
Grinspun, D, Bajnok I, Rey M. Delirium, *Dementia, and Depression in Older Adults: Assessment and Care*. Toronto, Canada: Registered Nurses' Association of Ontario; 2016.	Duplicate
National Guideline Clearinghouse. *Delirium, Dementia, and Depression in Older Adults: Assessment and Care*. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2016. Available from: https://www.guideline.gov. Accessed January 19, 2017.	Duplicate
National Institute for Health and Care Excellence. *Depression in Adults: Recognition and Management.* 2009. Available from: https://www.nice.org.uk/guidance/cg90/evidence. Accessed June 30, 2017.	Duplicate
Boltz M (Ed.). *Evidence-based Geriatric Nursing Protocols for Best Practice*. New York, NY: Springer; 2012.	Duplicate
Depression. University of Michigan Health System. NGC:008672.	Duplicate
Álvarez Ariza M, Atienza Merino G, Ávila González MJ, González García A, Guitián Rodrígue D. *GPC sobre el Manejo de la Depresión en el Adulto.* Madrid, Spain: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014.	Duplicate
National Guideline Clearinghouse. *Depression* (Singapore). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2012. Available from https://www.guideline.gov/summaries/summary/39324. Accessed October 19, 2016.	Duplicate
Austin M-P, Highet N, The Expert Working Group. *Mental Health Care in the Perinatal Period: Australian Clinical Practice Guideline*. Melbourne, Australia: Centre of Perinatal Excellence; 2017.	Duplicate
McDermott B, Baigent M, Chanen A, et al. *Clinical Practice Guidelines: Depression in Adolescents and Young Adults.* Melbourne, Australia: Agency for Healthcare Research and Quality; 2010.	Duplicate
Michigan Quality Improvement Consortium Guideline. *Primary Care Diagnosis and Management of Adults with Depression*. Detroit, MI: MQIC; 2018. Available from: http://mqic.org/guidelines.htm. Accessed October 19, 2016.	Duplicate
National Institute for Health and Clinical Excellence. *Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care.* Leicester, UK: British Psychological Society; 2005.	Duplicate
Michigan Quality Improvement Consortium Guideline. *Primary Care Diagnosis and Management of Adults with Depression*. Detroit, MI: MQIC; 2018. Available from: http://mqic.org/guidelines.htm. Accessed October 19, 2016.	Duplicate

Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs*. 2011;71(1):43–64. doi:10.2165/11587620-000000000-00000.	Duplicate
National Institute for Health and Care Excellence. *Common Mental Health Disorders. Identification and Pathways to Care*. London, UK: NICE; 2011.	Without pharmacological treatment
Grinspun, D, Bajnok I, Rey M. *Delirium, Dementia, and Depression in Older Adults: Assessment and Care*. Toronto, Canada: Registered Nurses' Association of Ontario; 2016.	Duplicate
Joffres M, Jaramillo A, Dickinson J, et al. Recommendations on screening for depression in adults. *CMAJ*. 2013;185(9):775–782. doi:10.1503/cmaj.130403.	Without pharmacological treatment
Boltz M (Ed.). *Evidence-based Geriatric Nursing Protocols for Best Practice*. New York, NY: Springer; 2012.	Duplicate
Patten SB. Updated CANMAT guidelines for treatment of major depressive disorder. *Can J Psychiatry*. 2016; 61(9):504–505. doi:10.1177/0706743716660034.	Without pharmacological treatment
Rush AJ, Aaronson ST, Demyttenaere K. Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive. *Aust N Z J Psychiatry*. 2019;53(2):109–118. doi:10.1177/0004867418808585.	Without pharmacological treatment
Frye MA. Clinical practice: bipolar disorder--a focus on depression. *N Engl J Med*. 2011;364(1):51–59.	Subject matter
Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2015;49(12):1087–1206. doi:10.1177/0004867415617657.	Duplicated
Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *J Clin Oncol*. 2014;32(15):1605–1619. doi:10.1200/JCO.2013.52.4611.	Subject matter
American Medical Directors Association. *Guideline Summary: Depression in the Long Term Care Setting.* Columbia, MD: AMDA; 2011.	Subject matter
Joffres M, Jaramillo A, Dickinson J, et al. Recommendations on screening for depression in adults. *CMAJ*. 2013;185(9):775–782. doi:10.1503/cmaj.130403.	Subject matter
Li M, Kennedy EB, Byrne N, et al. The management of depression in patients with cancer: a clinical practice guide. *J Oncol Pract*. 2016;12(8):747–756. doi:10.1200/JOP.2016.011072.	Subject matter
Ostacher MJ, Tandon R, Suppes T. Florida best practice psychotherapeutic medication guidelines for adults with bipolar disorder: a novel, practical, patient-centered guide for clinicians. *J Clin Psychiatry*. 2016;77(7):920–926. doi:10.4088/JCP.15cs09841. Available in:	Subject matter

http://www.embase.com/search/results?subaction=viewrecord &from=export&id=L611538719.	
Pfennig A, Bschor T, Falkai P, Bauer M. The diagnosis and treatment of bipolar disorder: recommendations from the current S3 guideline. *Dtsch Arztebl Int.* 110(6):92–100. doi:10.3238/arztebl.2013.0092.	Subject matter
Rosenblat JD, McIntyre RS. Treatment recommendations for DSM-5–defined mixed features. *CNS Spectr*. 2017;22(2):147–154. doi:10.1017/S1092852916000432.	Subject matter
Alexopoulos GS. Pharmacotherapy for late-life depression. *J Clin Psychiatry.* 2011;72(1):e04. doi:10.4088/JCP.7085tx2cj.	Not a CPG
Andreescu C, Reynolds CF III. Late-life depression: evidence-based treatment and promising new directions for research and clinical practice. *Psychiatr Clin North Am*. 2011;34(2):335–355. doi:10.1016/j.psc.2011.02.005.	Not a CPG
Arnow BA, Steidtmann D, Blasey C, et al. The relationship between the therapeutic alliance and treatment outcome in two distinct psychotherapies for chronic depression. *J Consult Clin Psychol*. 2013; 81(4):627–638. doi:10.1037/a0031530.	Not a CPG
Ayub-Dargél A, Masson M, Henry C. The RANZCP guidelines: managing mood disorders in the real world. *Aust N Z J Psychiatry*. 2016;50(12):1198–1199. doi:10.1177/0004867416676373.	Not a CPG
Bland P. Raising standards of care for patients with depression. *Practitioner*. 2011;255(1740):21–25.	Not a CPG
Boffin N, Bossuyt N, Declercq T, Vanthomme K, Van Casteren V. Incidence, patient characteristics and treatment initiated for GP-diagnosed depression in general practice: results of a 1-year nationwide surveillance study. *Fam Prac*. 2012;29(6):678–687. doi:10.1093/fampra/cms024.	Not a CPG
Bohra HM, Novak M. Depression in patients with chronic kidney disease. *CANNT J*. 2015;25(3):34–38.	Not a CPG
Busch FN, Sandberg LS. Combined treatment of depression. *Psychiatr Clin North Am.* 2012;35(1):165–179. doi:10.1016/j.psc.2011.10.002.	Not a CPG
Cohen A. The QOF, NICE, and depression. *Br J Gen Pract.* 2011;61(590):549. doi:10.3399/bjgp11X593785.	Not a CPG
Baumann S, Benson-Martin J, Cossie Q, et al. SASOP treatment guidelines for psychiatric disorders: eminence or evidence based? *S Afr J Psychiatr*. 2019;20(2):a529. doi10.4102/sajpsychiatry.v20i2.529.	Not a CPG
Cosgrove L, Shaughnessy AF, Wheeler EE, Austad KE, Kirsch I, Bursztajn HJ. The American Psychiatric Association's guideline for major depressive disorder: a commentary. *Psychother Psychosom*. 2012;81(3):186–188. doi:10.1159/000335523.	Not a CPG

Cuijpers P. Effective therapies or effective mechanisms in treatment guidelines for depression? *Depress Anxiety*. 2013;30(11):1055–1057. doi:10.1002/da.22205.	Not a CPG
Cuijpers P. Combined pharmacotherapy and psychotherapy in the treatment of mild to moderate major depression? *JAMA Psychiatry*. 2014;71(7):747–748. doi:10.1001/jamapsychiatry.2014.277.	Not a CPG
De Coteau PA, Byrne CD, Russell, V. The HSE/ICGP guidelines on the management of depression and anxiety disorders in primary care. *Ir Med J*. 2012;105(7):251.	Not a CPG
Desseilles M, Witte J, Chang TE, et al. Assessing the adequacy of past antidepressant trials: a clinician's guide to the antidepressant treatment response questionnaire. *J Clin Psychiatry*. 2011;72(8):1152–1154. doi:10.4088/JCP.11ac07225.	Not a CPG
Canadian Agency for Drugs and Technologies in Health. *Diagnosing, Screening, and Monitoring Depression in the Elderly: A Review of Guidelines*. Ottawa, ON: CADTH; 2015.	Not a CPG
Canadian Agency for Drugs and Technologies in Health. *Antidepressants in Elderly Patients with Major and Minor Depression: A Review of Clinical Effectiveness and Guidelines*. Ottawa, ON: CADTH; 2015.	Not a CPG
Gensichen J, Härter M, Klesse C, et al. Germany's national clinical practice guideline (S3) for unipolar depression—What is important for family practice? *ZFA*. 2011;87(5):223–230. doi:10.3238/zfa.2011.0223.	Not a CPG
Geoffroy PA, Bellivier F. The RANZCP mood disorders guidelines: an easy step-by-step toolbox for daily practice. *Aust N Z J Psychiatry*. 2016;50(10):1014–1015. doi:10.1177/0004867416667829.	Not a CPG
Gitlin M. The Royal Australian and New Zealand College of Psychiatrists clinical guidelines for mood disorders: kudos and quarrels. *Aust N Z Psychiatry*. 2016;50(10):937–938. doi:10.1177/0004867416668038.	Not a CPG
Grobler, G. An overview of depression treatment guidelines. Abstracts 2nd African College of Neuropsychopharmacology Congress 30–31 July 2016 Stellenbosch, Western Cape, South Africa. *Acta Neuropsychiatr*. 2016;28(s3):1–15. doi:10.1017/neu.2016.37.	Not a CPG
Heilmann KE, Wagner M, Riedel-Heller S, Maier W, Jessen F. Treating late life depression with antidepressants: a summary of recommendations in international guidelines. *Fortschr Neurol Psychiatr*. 2015;83(7):381–391. doi:10.1055/s-0035-1553315.	Not a CPG
Horgan D, Dodd S. Combination antidepressants—use by GPs and psychiatrists. *Aust Fam Physician*. 2011;40(6):397–400.	Not a CPG
Kasper S. Editorial. *World J Biol Psychiatry*. 2013;14(5):333. doi:10.3109/15622975.2013.819703.	Not a CPG

Kendall T, Pilling S, Glover N, Taylor C. Guidelines in mental health – national and international perspectives. I*nt Rev Psychiatry*. 2011;23(4):314–317. doi:10.3109/09540261.2011.607431.	Not a CPG
Kongsuk T. Clinical practice guideline major depressive disorder for general practitioners. *Value Health*. 2013;16(7): A695. doi:10.1016/j.jval.2013.08.2091.	Not a CPG
Kurian BT, Grannemann B, Trivedi MH. Feasible evidence-based strategies to manage depression in primary care. *Curr Psychiatr Rep*. 2012;14(4):370–375. doi:10.1007/s11920-012-0290-y.	Not a CPG
Laux G. Update treatment of depression—S3 Guideline, internet-based psychotherapy, antidepressants and driving ability. *Nervenheilkunde*. 2016;35(10):691–696. doi:10.1055/s-0037-1616433.	Not a CPG
Leadholm AKK, Rothschild AJ, Nolen WA, Bech P, Munk-Jørgensen P, Østergaard SD. The treatment of psychotic depression: is there consensus among guidelines and psychiatrists? *J Affect Disord*. 145(2): 214–220. doi:10.1016/j.jad.2012.07.036.	Not a CPG
Malhi G, Oakley-Browne M, Hay P. Clinical practice guidelines project (CPG project) overview. *Aust N Z J Psychiatr*. 2015;49(Supp 1):30. doi:10.1177/0004867415578344.	Not a CPG
Manning JS, Jackson WC. Providing guideline-concordant assessment and monitoring for major depression in primary care. *J Clin Psychiatr*y. 2015;76(1):e3. doi:10.4088/JCP.13013tx7c.	Not a CPG
Mathys M, Mitchell BG. Targeting treatment-resistant depression. *J Pharm Pract*. 2011;24(6):520–533. doi:10.1177/0897190011426972.	Not a CPG
Morris DW, Trivedi MH. Measurement-based care for unipolar depression. *Curr Psychiatry Rep*. 2011;13(6);446–458. doi:10.1007/s11920-011-0237-8.	Not a CPG
Nelson JC. Foreword. *CNS Drugs*. 2013;27:3–4. doi:10.1007/s40263-012-0027-9.	Not a CPG
Nutt DJ. Highlights of the international consensus statement on major depressive disorder. *J. Clin Psychiatry*. 2011;72(6):e21. doi:10.4088/JCP.9058tx2c.	Not a CPG
Ogasawara K, Ozaki N. Review of the new treatment guideline for major depressive disorder by the Japanese Society of Mood Disorders. *Brain Nerve*. 2012;64(10):1159–1165. In Japanese.	Not a CPG
Oldham J. Fine-tuning our treatment strategies. *J Psychiatr Pract*. 2011;17(3):157. doi:10.1097/01.pra.0000398408.13750.8d.	Not a CPG
Pai N. Are the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders	Not a CPG

meeting the needs of clinicians? *Aust N Z J Psychiatry*. 2016;50(10):1015–1016. doi:10.1177/0004867416667828.	
Patkar AA, Pae C-U. Atypical antipsychotic augmentation strategies in the context of guideline-based care for the treatment of major depressive disorder. *CNS Drugs*. 2013;27(Suppl 1):S29–S37. doi:10.1007/s40263-012-0031-0.	Not a CPG
Rawlins M. Ten years of NICE mental health guidelines. *Int Rev Psychiatry*. 2011;23(4):311–313. doi:10.3109/09540261.2011.606804.	Not a CPG
Reisdorf S. Revision of the national health care guidelines on unipolar depression. *Med Monatss Pharm*. 2016;39(4):171–172.	Not a CPG
Roberge P, Fournier L, Brouillet H, et al. A provincial adaptation of clinical practice guidelines for depression in primary care: a case illustration of the ADAPTE method. *J Eval Clin Pract*. 2015;21(6):1190–1198. doi:10.1111/jep.12404.	Not a CPG
Schuklenk U, Vathorst SVD. Treatment-resistant major depressive disorder and assisted dying. *J Med Ethics*. 2015;41(8), 577–583. doi:10.1136/medethics-2014-102458.	Not a CPG
Schulte-Körne G, Krick K. In reply. *Dtsch Arztebl Int*. 2014;111(18):330. doi:10.3238/arztebl.2014.0330c.	Not a CPG
Tomba E, Fava GA. Treatment selection in depression: the role of clinical judgment. *Psychiatr Clin North Am*. 2012;35(1):87–98. doi:10.1016/j.psc.2011.11.003.	Not a CPG
Treuer T, Liu C-Y, Salazar G, et al. Use of antidepressants in the treatment of depression in Asia: guidelines, clinical evidence, and experience revisited. *Asia Pac Psychiatry*. 2013;5(4):219–230. doi:10.1111/appy.12090.	Not a CPG
Tundo A, Calabrese JR, Proietti L, De Filippis R. Short-term antidepressant treatment of bipolar depression: are ISBD recommendations useful in clinical practice? *J Affect Disord*. 2015;171:155–160. doi:10.1016/j.jad.2014.09.019.	Not a CPG
Van Avendonk M, van Weel-Baumgarten E, van der Weele G, Wiersma T, Burgers JS. Summary of the Dutch College of General Practitioners' practice guideline "Depression". *Ned Tijdschr Geneeskd*. 2012;156(38):A5101.	Not a CPG
Vinberg M, Levinsen MF, Kessing LV. Treatment-resistant depression is treatable. *Ugeskr Laeger*. 2011;173(9):651–654.	Not a CPG
Wang HR, Bahk WM, Park YM, et al. Korean medication algorithm for depressive disorder: comparisons with other treatment guidelines. *Psychiatry Investig*. 2014;11(1):1–11. doi:10.4306/pi.2014.11.1.1.	Not a CPG
Won E, Park SC, Han KM, et al. Evidence-based, pharmacological treatment guideline for depression in Korea, revised edition. *J Korean Med Sci*. 2014;29(4):468–484. doi:10.3346/jkms.2014.29.4.468.	Not a CPG

Xiang YT, Hu C, Wang G, et al. Prescribing patterns of antidepressants, antipsychotics and mood stabilizers in bipolar patients misdiagnosed with major depressive disorder in China. *Hum Psychopharmacol*. 2012;27(6):626–631. doi:10.1002/hup.2262.	Not a CPG
Yang J, Han C, Yoon HK, et al. Experiences and barriers to implementation of clinical practice guideline for depression in Korea. *BMC Psychiatry*. 2013;13:150. doi:10.1186/1471-244X-13-150.	Not a CPG
Zimmerman M. Symptom severity and guideline-based treatment recommendations for depressed patients: implications of DSM-5's potential recommendation of the PHQ-9 as the measure of choice for depression severity. *Psychother Psychosom.* 2012;81(6):329–332. doi:10.1159/000342262.	Not a CPG
Zimmerman M, Martinez JH, Friedman M, Boerescu DA, Attiullah N, Toba C. How can we use depression severity to guide treatment selection when measures of depression categorize patients differently? *J Clin Psychiatry*. 2012;73(10):1287–1291. doi:10.4088/JCP.12m07775.	Not a CPG
Malhi GS, Outhred T, Hamilton A, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Med J Aust.* 2018;208(4):175–180. doi:10.5694/mja17.00659.	Not a CPG
Evidence-Based Clinical Practice Guidelines for Depression in Adults on Traditional Korean Medicine; 2016.	Not found
S3-Leitlinie/Nationale Versorgungs Leitlinie Unipolare Depression; 2015. In German.	Language
Depression. Adapted Evidence-based Guideline. Ucrania; 2014 - Депресія. Адаптованаклінічнанастанова. In Ukrainian.	Language
[*Depressive Disorder. Depressie* (M44)]; 2012. In Dutch.	Language
Herrmann M, Gensichen J. Guidelines in general practice: the example depression. *Psychiatrie*. 2015;66:119–124.	Language
Kuroki T, Tanaka T. [Threshold of application of antidepressant drugs for treatment of depressive disorder]. *Seishin Shinkeigaku Zasshi*. 2015;117(4):269–276. In Japanese.	Language
Semba J. [Proper use of novel antidepressants in psychiatric clinical practice]. *Seishin Shinkeigaku Zasshi*. 2014;116(2):138–143. In Japanese.	Language
Yamada K. [Evidence of treatment for depressive episodes of bipolar disorder]. *Seishin Shinkeigaku Zasshi*. 2011;113(9):873–879. In Japanese.	Language
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Clinical Practice Guidelines: Depression in Adolescents and Young Adults. Melbourne, Australia: NHMCRC; 2015.	Focus on special groups
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Galician Health Technology Assessment Agency. *Clinical Practice Guideline on the Management of Major Depression in Adults*. Santiago de Compostela, Spain: Galician Health Technology Assessment Agency; 2008.	Outdated
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Lam RW, Parikh SV, Michalak EE, Dewa CS, Kennedy SH. Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Ann Clin Psychiatr*. 2015;27(2):142–149.	Outdated
Agency for Healthcare Research and Quality. *Detecting Depression in Older Adults with Dementia*. Ann Arbor, MI: University of Michigan Health System; [s.d].	Outdated
Adult Depression in Primary Care. Bloomington, MN: ICSI; 2013.	Outdated
Galletly C, Castle D, Dark F, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Aust N Z J Psychiatry*. 2016;50(5):410–472. doi:10.1177/0004867416641195.	Outdated

Karyotaki E, Smit Y, Cuijpers P, et al. *The Long-term Efficacy of Psychotherapy, Alone or in Combination with Antidepressants, in the Treatment of Adult Major Depression. Good Clinical Practice (GCP).* Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE); 2014. Available from: https://kce.fgov.be/sites/default/files/atoms/files/KCE_230_Depression_Report_0.pdf. Accessed June 30, 2017.	Focus on psychotherapy

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5 (although not an explicit PICO)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	CRD42016043364
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 Appendix 2 8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11 Table 4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Quality of clinical practice guidelines for inadequate first-line treatment for depression according to AGREE checklist and comparison of recommendations: a systematic review

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Quality of clinical practice guidelines for inadequate first-line treatment for depression according to AGREE II checklist and comparison of recommendations: a systematic review

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ABSTRACT

Objective To assess similarities and differences in the recommended sequence of strategies among the most relevant clinical practice guidelines (CPGs) for the treatment of depression in adults with inadequate response to first-line treatment.

Data Sources We performed a systematic review of the literature spanning January 2011 to August 2020 in Medline, Embase, Cochrane, and 12 databases recognized as CPGs repositories. CPGs quality was assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE) II.

Study Selection The eligibility criteria were CPGs that described pharmacological recommendations for treating depression for individuals aged 18 years or older in outpatient care setting. We included CPGs considered of high-quality (≥ 80% in domain 3 of AGREE II) or recognized as clinically relevant.

Data Extraction Two independent researchers extracted recommendations for patients who did not respond to first-line pharmacological treatment from the selected CPGs.

Results We included 46 CPGs and selected 8, of which 5 were considered high-quality (≥ 80% in domain 3 of AGREE II) and 3 were recognized as clinically relevant. Three CPGs did not define inadequate response to treatment and 3 did not establish a clear sequence of strategies. The duration of treatment needed to determine that a patient had not responded was not explicit in 3 CPGs and was discordant in 5 CPGs. Most CPGs agree in reassessing the diagnosis, assessing the presence of comorbidities and adherence to treatment, and increase in dosage as first steps. All CPGs recommend psychotherapy, switching and considering augmentation / combining antidepressants.

Conclusion Relevant CPGs present shortcomings in recommendations for non-responders to first line antidepressant treatment including absence and divergencies in definition of inadequate response and sequence of recommended strategies. Overall,

most relevant CPGs recommend reassessing the diagnosis, evaluate comorbidities and adherence to treatment, increase dosage of antidepressants and psychotherapy as first steps.

Strengths and limitations of this study

- All included clinical practice guidelines (CPGs) were assessed for quality using the recognized tool "Appraisal of Guidelines for Research & Evaluation (AGREE) II" in which a careful training of appraisers was conducted.
- The study was based on a comprehensive literature search about the pharmacological treatment of depression conducted in 15 databases using a sensitive strategy.
- The main comparison of management strategies was focused on the eight most relevant CPGs leading to a high-quality synopsis.
- The inclusion of three CPGs often used in clinical practice (from The Canadian Network for Mood and Anxiety Treatments – CANMAT; from the American Psychiatric Association – APA-Psychiatry; and from the US Department of Veterans Affairs (VA), US Department of Defense (DOD), enabled a broader discussion of clinical questions mentioned in the CPGs.
- The main limitation was that the inclusion had been restricted to papers written in English, Portuguese, or Spanish.

INTRODUCTION

Depression is a mental health problem with severe consequences for afflicted individuals. This mental disorder results in substantial professional, economic, social, and personal losses for affected individuals owing to its incapacitating nature.[1] The World Health Organization[2](WHO) estimates that over 300 million people globally are affected by depression, which is the main contributor to 800,000 suicides annually worldwide. Additionally, depression can cause critical social problems, as depressed individuals are less productive, resulting in additional costs to their employers and governments.[3]

The number of depressed persons has increased considerably.[4] This situation overburdens the healthcare system and generates a greater need for resource optimization.[5] Thus, developing evidence-based interventions to achieve effective results is a pressing challenge in the mental health field.[6] Moreover, owing to the 2019 coronavirus (COVID-19) pandemic, an increase in mental illnesses is expected, perhaps persisting for years. There will be an even greater need to optimize resources for dealing with this significant challenge.[7] A survey by the WHO[8] showed that the COVID-19 pandemic had suspended essential mental health services in about 93% of countries worldwide while the population increasingly needs mental health care.

Clinical practice guidelines (CPGs) are fundamental to optimize these mental health resources, which will be in greater demand with the increased incidence of depression.[9] These CPGs contain recommendations for optimizing patient healthcare and have been developed by reviewing interventions and a cost-benefit analysis for each clinical health condition.[10] Hence, they enable the development of objective clinical decisions, help decrease clinical variability, educate patients and professionals on updated best practices, and improve the cost-effectiveness of healthcare.[11]

Among the interventions proposed in the CPGs, evidence-based pharmacotherapy is one of the strategies used to treat depression.[12] However, a previous study demonstrated a lack of information regarding the best approaches when pharmacological treatment for first-line depression fails.[13] Considering that the response to first-line treatment is only moderate (40%–60%) and remission after antidepressant treatment is achieved in only a minority of patients (30%–45%), there is a need to investigate such gaps more thoroughly to improve CPGs.[14]

Additionally, there is a lack of clarity in the CPGs on clinical actions, and divergence among different approaches about the sequence of strategies for depressed individuals who presented an inadequate response to first-line treatment.[13] Thus, to improve mental health professionals' clinical recommendations and provide better healthcare to patients, in-depth evaluation of the CPGs recommendations for patients who do not respond adequately to initial pharmacological interventions is necessary.

Study aims

Here we aimed to assess similarities and differences in the recommended sequence of strategies among the most relevant clinical practice guidelines for the treatment of depression in adults who have shown an inadequate response to first-line treatment.

MATERIALS AND METHODS

A broad health search was conducted to explore the methodological quality and transparency of CPGs for the pharmacological treatment of non-communicable diseases, including depression. We updated the search of a previous PROSPERO systematic review (CRD42016043364)[15] and conducted an analysis specifically assessing CPGs that can be used by health professionals for the pharmacological treatment of adults with depression in outpatient settings.

We used the second version of the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument (https://www.agreetrust.org) to evaluate the quality of the CPGs identified in the research—a fundamental step of a systematic review. Additionally, the recommendations of high-quality CPGs or those most commonly used in clinical practice[16] were compared to a method applied in a previous study published by the authors.[13]

Search data source

A comprehensive search was conducted on PubMed, Embase, and the Cochrane Library for CPGs published from January 1, 2011, to August 22, 2020 (Appendix 1). We consulted twelve databases traditionally recognized as CPGs repositories.[13,17,18] Mendeley® software was used to conduct this search and remove duplicates. In December 2021, we searched the literature to update the included CPGs.

Eligibility criteria

Only CPGs that made pharmacological recommendations for treating depression in individuals aged 18 years or older were included. The following CPGs were excluded: those that did not have the full text available in Portuguese, English, or Spanish; those that focused on psychotherapeutic treatment or neuromodulation; and those for specific populations, such as patients with cancer, multiple sclerosis, or pregnant or lactating women. CPGs for the treatment of bipolar depression only were also excluded. The latest versions of CPGs found on the original authors' websites were included. Two evaluators independently read the titles and abstracts of the retrieved articles and—if the content met the eligibility criteria—evaluated the full text. Discrepancies were resolved by one of the authors (GCHFM), who acted as the third evaluator. The latest version of each CPG, and all related complementary documents, were sent to the evaluators for a quality assessment using the AGREE II. To be included, the CPGs should have a score ≥ 80% or domain 3

of AGREE II - considered of high-quality; or were among the those most relevant in clinical practice either by being the most used ones,[16] or developed by an institution considered as a leader in developing CPGs.

Extraction of general data and CPGs quality evaluation

Previously validated forms[18] were used by two independent reviewers for data extraction. A third reviewer resolved the discrepancies. The following data were extracted: type of organization that produced the CPG (government organization or specialized society), country, method used to classify the evidence, and the CPG development method (whether done using adaptation methodology or other methods). Three independent researchers (FCG, IBS, and ST) evaluated the CPGs using the six AGREE II domains. The AGREE II contains 23 items grouped into six domains and two global classifications (general evaluation items). Each AGREE II domain evaluates a different dimension of CPG quality:[19] scope and purpose (domain 1), stakeholder involvement (domain 2), rigour of development (domain 3), clarity of presentation (domain 4), applicability (domain 5), and editorial independence (domain 6). A Likert scale ranging from 1 to 7 was used to evaluate the 23 items. Each reviewer entered an evaluation into the AGREE II platform for each item. The calculation was made automatically on the platform for each quality domain.

Further, owing to the substantial heterogeneity of the general evaluation items, our protocol defined the items would not be included in the analyses. We decided to primarily focus on domain 3. All evaluators underwent rigorous training on the AGREE II application before making the quality assessment (details of this training have been previously published).[18] The evaluators discussed discrepancies of two or more points until consensus was reached. The score was calculated individually for each domain.

Comparison of recommendations

The recommendations of high-quality CPGs were compared. The inclusion criteria were: a score of 80% or above in domain 3 of AGREE II, CPGs that were the most commonly used in clinical practice, and the ones developed by an important CPGs developer institution. Domain 3 (methodological rigour) was used to classify a CPG as "high-quality" since this is the most important item regarding the reliability of the recommendations.[20] Two independent researchers extracted all recommendations from CPGs that were included. The final version of the comparative tables of recommendations were achieved after two rounds of discussion. The recommendations were grouped by the following main topics: terminology for responsiveness and recommended management strategies. The terminologies and sequences of the therapeutic strategies were compared between the CPGs and the strategies and terminologies that the CPGs had in common were synthesized in a third table.

Patient and Public Involvement

No patients were involved in this study.

RESULTS

We identified 1949 records in the database search – Medline (n = 689), Cochrane (n = 105), and Embase (n = 1155), and 44 additional records through the other 12 specific websites for CPGs. After removing 165 duplicates using Mendeley®, 1993 documents remained. From those we included 46 CPGs[21-66] for quality assessment and selected eight for analysis of recommendation (Figure 1). Appendix 2 includes the reasons for including/excluding documents. Five CPGs that presented an AGREE-II domain 3 score ≥ 80% were considered high-quality and selected. Two others (from The Canadian Network for Mood and Anxiety Treatments – CANMAT[21] and from the American

Psychiatric Association – APA[22]) were also selected based on their widespread acceptance[16] and an additional one (US Department of Veterans Affairs (VA), US Department of Defense (DOD) – VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder)[23] for been considered by the National Academy of Medicine (US) as a leader in CPG development. The eight CPGs included with their scores in the AGREE-II domain 3 were: Depresión en Personas de 15 Años y Más, from the Ministerio de Salud Chile, score = 89%;[24] Guía de Práctica Clínica (GPC): Detección Temprana y Diagnóstico del Episodio Depresivo y Trastorno Depresivo Recurrente en Adultos: Atención Integral de los Adultos con Diagnóstico de Episodio Depresivo o Trastorno Depresivo Recurrente from the Ministerio de Salud Colombia, score = 86%;[25] Depression in adults: recognition and management from the National Institute for Health and Care Excellence (NICE) -United Kingdom, score = 84%;[26] Depression, Adults in Primary Care from Institute for Clinical Systems Improvement (ICSI) Health Care Guideline – United States of America (US), score = 81%;[27] Clinical Practice Guideline for the Treatment of Depression across Three Age Cohorts from the American Psychology Association (APA-Psychology) – United States of America (US), score = 81%;[28] VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder from the US Department of Veterans Affairs (VA), US Department of Defense (DOD), score = 78%;[23] Clinical guidelines for the management of adults with major depressive disorder from the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 – from Canada, score = 54%;[21] Practice Guideline for the Treatment of Patients with Major Depressive Disorder from the American Psychiatric Association, Third Edition (APA-Psychiatry) – from US, score = 46%.[22]

Table 1 describes the characteristics of all the 46 CPGs identified for quality assessment. There is considerable quality variation among CPGs. For instance, the

AGREE's domain 3 median value is 46.5% ranging from 6% to 89%. Table 2 present a detailed description of the management strategies proposed by the most relevant CPGs concerning inadequate response to first-line treatment.

Table 1 - Characteristics of clinical practice guidelines (CPGs) identified for quality assessment and AGREE-II scores sorted in decreasing order of Domain 3 scores (n=46).

CPG; Author, year	AGREE-II Domain Score (%)						Organization	Location	Grading*	Development**
	1	2	3	4	5	6				
MS Chile, 2012[24]	83	76	89	94	57	17	Governmental	Chile	GRADE***	New
MS Colombia, 2015[25]	100	85	86	100	96	92	Governmental	Colombia	GRADE	Adapted
NICE, 2018[26]	89	83	84	81	71	75	Governmental	England	GRADE	New
Trangle et al., 2016[27]	96	78	81	91	72	97	Consortium	US	GRADE	New
APA, 2019[28]	91	67	81	80	57	83	Specialty society	US	GRADE	New
VA/DoD, 2016[23]	93	76	78	94	38	58	Specialty society	US	GRADE	New
KPCMI, 2012[29]	83	63	76	93	46	58	Specialty society	US	GRADE	Adapted
Minsan Spain, 2014[30]	94	93	70	91	57	53	Governmental	Spain	Own method	New
RNAO, 2016[31]	72	74	69	80	76	86	Specialty society	Canada	Own method	New
Perez-Bryan et al., 2011[32]	70	44	69	80	50	69	Governmental	Spain	GRADE	New
Qaseem et al., 2016[33]	80	39	69	70	32	67	Specialty society	US	GRADE	New
IMSS, 2011[34]	87	46	69	83	14	67	Governmental	Mexico	Own method	Adapted
IMSS, 2015[35]	81	43	69	80	32	31	Governmental	Mexico	Several	Adapted
IMSS, 2016[36]	94	56	63	81	42	64	Governmental	Mexico	Several	New
Chua et al., 2012[37]	78	72	60	89	50	28	Governmental	Singapore	Own method	Adapted
Malhi et al., 2015[38]	74	63	58	78	24	67	Governmental	Australia	NA	New
Driot et al., 2017[39]	69	30	56	72	11	83	Independent authors	France	NA	New
Bauer et al., 2013[40]	61	54	54	83	32	75	Governmental	Several	Own method	New
Kennedy at al., 2016[21]	63	48	54	89	26	53	Specialty society	Canada	Own method	New
Dua et al., 2011[41]	69	74	50	74	29	75	Governmental	Several	GRADE	New
McIntyre et al., 2017[42]	87	56	48	83	32	69	Specialty society	US	Own method	New
Bauer et al., 2015[43]	69	48	47	61	28	75	Specialty society	Several	Own method	New
MH Malasia, 2019[44]	81	50	47	70	54	78	Governmental	Malaysia	SIGN adapted	New
Gelenberg et al., 2010[22]	48	43	46	83	44	42	Specialty society	US	Own method	New
Cleare et al., 2015[45]	67	57	40	69	13	58	Specialty society	England	Own method	New
Ruberto et al., 2020[46]	43	11	35	39	1	72	Independent	US	NA	New
BC Guidelines Canada, 2013[47]	85	37	35	85	39	42	Governmental	Canada	Own method	New
Giakoumatos et al., 2019[48]	61	19	33	83	26	75	Specialty society	US	NA	New

Bauer et al., 2017[49]	56	41	23	76	21	50	Specialty society	Several	Own method	New
Bennabi et al., 2019[50]	50	33	22	65	13	67	Specialty society	France	NA	New
Grobler, 2013[51]	50	48	19	67	13	19	Specialty society	South Africa	NA	New
Connolly et al., 2011[52]	63	17	17	52	13	72	Independent	US	NA	New
Wang et al., 2017[53]	56	13	17	43	6	58	Specialty society	Korea	NA	New
Park et al., 2019[54]	33	22	17	50	18	31	Independent	US	NA	New
Voineskos et al., 2020[55]	44	11	15	50	10	22	Independent authors	Canada	NA	New
Voineskos et al., 2018[56]	54	39	15	65	8	42	Independent	US	NA	New
Piotrowski et al., 2017[57]	54	26	15	72	25	50	Specialty society	Poland	NA	New
Bayes et al., 2019[58]	46	22	14	48	7	33	Independent authors	Australia	NA	New
Malhi et al., 2013[59]	44	20	13	63	17	39	Governmental	Australia	NA	New
Mulsant et al., 2014[60]	50	28	13	61	8	36	Governmental	Canada	NA	New
Avasthi et al., 2018[61]	70	24	12	80	36	0	Independent authors	India	NA	New
Möller et al., 2012[62]	28	15	12	11	10	33	Governmental	Several	NA	New
Busch et al., 2012[63]	46	11	10	65	15	17	Independent authors	US	NA	New
Taylor, 2014[64]	41	7	8	57	8	33	Independent authors	US	NA	New
Sánchez et al., 2019[65]	54	24	6	61	8	33	Independent authors	Spanish	NA	New
Gautam et al., 2017[66]	39	20	6	57	15	0	Independent authors	India	NA	New

CPG = Clinical Practice Guideline, AGREE-II = Appraisal of Guidelines for Research & Evaluation, MS = Ministerio de Salud (Ministry of Health), NICE = National Institute for Health and Care Excellence, APA = American Psychological Association, VA/DoD = US Department of Veterans Affairs (VA), US Department of Defense (DoD), *KPCMI* = Kaiser Permanente Care Management Institute, RNAO = Registered Nurses' Association of Ontario, IMSS = Instituto Mexicano del Seguro Social, SIGN= Scottish Intercollegiate Guidelines Network, MH = Ministry of Health, BC = British Columbia, US = United States of America, NA = not available.

*Grading of evidence system, **Method of clinical practice guideline development, ***modified version of GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Table 2 -Strategies for inadequate response to first-line treatment of depression according to most relevant CPGs.

CPG; Author, year	Terminology for responsiveness	Recommended strategies
MS Chile, 2012[24]	Refractory or resistant to treatment: no appropriate response to pharmacotherapy under usual dosage or when there is poor or inadequate response to one or more treatments Remission: absence of signs and symptoms for 2 months	1. Reevaluation of the diagnosis 2. Adjusting dosage 3. Switching to a different antidepressant 4. Augmentation with a second medication (lithium, liothyronine or second antidepressant) 5. Combining antidepressants
MS Colombia, 2015[25]	Refractory or resistant to treatment: absence of substantial remission of depressive symptoms or no improvement of social functioning with trial of pharmacotherapy at adequate duration and dosage. Remission: the patient responds to treatment in the initial or acute phase (within 12 weeks) and does not present further relapses in the continuation and follow-up phase. Response: defined as a 50% decrease in the score on a symptom scale depressives	Reevaluate adherence diagnosis and adverse events, adjusting dosage, add psychotherapy, switching to a different antidepressant, combining antidepressants, augmentation with a second medication (lithium or thyroid hormone)
NICE, 2018[26]	Inadequate response: no clear definition is presented. Remission: complete relief of symptoms	1. Check adherence and adverse events 2. Increase the frequency of appointments and monitor results 3. Consider reintroducing previous treatments (increase the dose) 4. Consider switching to an alternative antidepressant 5. Combining medications or augmentation 6. Combined psychological and drug treatment

Trangle et al., 2016[27] (ICSI)	Partial response: 25-50% reduction in symptoms Response: > 50% reduction in symptom Remission: devoid of symptoms.	1. Reassessment of patient/family engagement and adherence 2. Optimize antidepressant dose 3. Switching to a different antidepressant 4. Adding, switching or substituting treatment modality 5. Adding cognitive psychotherapy or adding another medication (buspirone or bupropion) 6. Reevaluating the diagnosis and the possibility of a bipolar diagnosis 7. Check comorbidities and/or substance abuse (inclusion referral to specialized care) 8. Augmentation therapy: augmentation with lithium, antipsychotics or triiodothyronine (T3) and combination of antidepressants adding bupropion or buspirone, mirtazapine + SSRI, TCA + SSRI 9. Other strategies such as electroconvulsive therapy and hospitalization
APA-Psychology, 2019[28]	Partial response and no response: no clear definition is presented. Remission: no longer having symptoms Response: reduction in depressive symptoms	1. Switch from antidepressant medication alone to cognitive therapy alone 2. Switch from antidepressant medication alone to another antidepressant medication 3. Add psychotherapy (interpersonal psychotherapy, cognitive-behavioral therapy, or psychodynamic therapy) 4. Augment with another antidepressant medication (do not include augment with other medicines)

VA/DoD, 2016[23]	Partial response: <50% improvement in symptoms Response: improvement > 50% PHQ scores Remission: PHQ score ≤ 4 for at least one month Recuperation: PHQ score ≤ 4 for at least one month No response: no clear definition is presented.	Reevaluation of the diagnosis, comorbidities and adherence, adjusting dosage, augmentation of drugs, switching to another monotherapy (medication or psychotherapy), augmentation with a second medication including antidepressant, antipsychotic, lithium, T3 or psychotherapy.
Kennedy at al., 2016[21] (CANMAT)	Partial response: 25-49% reduction in symptom scores. No response: <25% reduction in symptom scores. Inadequate response: partial response and no response	1. Optimize antidepressant by increasing dose. 2. Consider adjunctive use of psychological and neurostimulation treatments. 3. Switch to an antidepressant with superior efficacy. 4. Add an adjunctive medication, either combination with other antidepressant or augmentation with other medication (e.g., triiodothyronine). 5. Consider switch to a second-line or third-line antidepressant. 6. Consider longer evaluation periods for improvement. 7. Increase dose if not at maximal doses. 8. Consider a chronic disease management approach, with less emphasis on symptom remission and more emphasis on improvement in functioning and quality of life.
Gelenberg et al., 2010[22] (APA-Psychiatry)	No response and partial response: no clear definition is presented.	During initial weeks - assess adherence, consider increasing medication dosage, and increase intensity of psychotherapy. For severe cases consider electroconvulsive therapy. At 4 to 8 weeks - Switch to a different antidepressant, change to or augmentation with psychotherapy, augmentation therapy with other

		antidepressant or other medicine, or electroconvulsive therapy.

CPG = Clinical Practice Guideline, AGREE-II = Appraisal of Guidelines for Research & Evaluation, MS = Ministerio de Salud, NICE = National Institute for Health and Care Excellence, ICSI= Institute for Clinical Systems Improvement; SSRI= Serotonin Selective Reuptake Inhibitor, TCA= Tricyclic Antidepressants, APA-Psychology = American Psychological Association, VA/DoD = US Department of Veterans Affairs (VA), US Department of Defense (DoD), PHQ=Patient Health Questionnaire, CANMAT= Canadian Network for Mood and Anxiety Treatments, APA-Psychiatry= American Psychiatric Association, NA = not available.

Terminology for responsiveness to the first line treatment and clear definition of terminology varied among CPGs. We found the terms remission,[23-28]response,[23,25,27,28] partial response,[21,23,27] no response,[21] inadequate response,[21] and refractory or resistant to treatment[24,25] (Table 2). Among the 8 most relevant CPGs, 4 (50%) used the terms but did not present a clear definition of them[22,23,26,28] (Table 2). Three (37.5%) CPGs also did not establish the length of treatment time needed to declare an inadequate response[23,24,28].

Most CPGs recommended as first steps to assess treatment adherence, reassess diagnosis and / or evaluate comorbidities (6/8, 75%). Majority of CPGs emphasized the importance of adjusting antidepressant dose (7/8, 87.5%) in cases where patients do not respond to first-line treatment. However, only the NICE[26] and CANMAT[21] CPGs stablish the time that should be waited specifically for increasing the dose; CANMAT: 2–4 weeks and NICE: 3–4 weeks. Adding psychotherapy was recommended by seven (87.5%) CPGs; three (37.5%) recommended neurostimulation and 4 (50%) switching from antidepressants to non-pharmacological treatment. Other recommendations, although less frequently mentioned, were to assess the occurrence of side effects (3/8, 37.5%; the APA-Psychiatry guideline[22] specify that replacing the drug should be considered), check substance abuse (3/8, 37.5%), increase the frequency of appointments (2/8, 25%), try previous treatments (1/8, 12.5%), and consider longer periods for improvement evaluation (1/8, 12.5%) (Table 3). All CPGs included the recommendation of switching antidepressants and adding other medicines. Some CPGs used the term combination for the use of two antidepressants and augmentation for adding another type of medicine to an antidepression while others did not make such distinction. The APA-Psychology[28] included the possibility of adding another antidepressant but did not include the possibility of adding other medicines. Six CPGs recommended switching to another antidepressant before combining or augmentation strategies.[21,23,24,26–28] Regarding

combining and augmentation, only the MS Chile guideline[24] stablished a sequency between them, recommending first augmentation and then combination. Most CPGs are congruent with the inclusion of antipsychotics, lithium and T3 as augmentation strategies to antidepressant treatment.

Table 3 – Summary of used definitions and strategies for inadequate response to first-line treatment among most relevant CPGs

Items	Author of the CPG							
	MS Chile, 2012[24]	**MS Colombia, 2015[25]**	**NICE, 2018[26]**	**Trangle et al., 2016[27] (ICSI)**	**VA/DoD, 2016[23]**	**APA-Psychology, 2019[28]**	**Kennedy at al., 2016[21] (CANMAT)**	**Gelenberg et al., 2010[22] (APA-Psychiatry)**
Clear treatment response definition								
no response							✓	
inadequate response							✓	
Remission	✓	✓	✓	✓	✓	✓		
response		✓		✓	✓	✓		
partial response				✓	✓		✓	
refractory or resistant	✓	✓						
Length of treatment time needed to declare an inadequate response (weeks)	-	3	4	6	-	-	2 - 4	4 - 8
Time that should elapse before increasing the dose;	-	-	3 - 4	-	-	-	2 - 4	-
Management of inadequate response or resistant depression								
switching antidepressants	✓	✓	✓	✓	✓	✓	✓	✓
consider augmentation/combining drugs	✓	✓	✓	✓	✓	✓	✓*	✓*
dosage adjustment	✓	✓	✓	✓	✓		✓	✓

add psychotherapy to pharmacotherapy		✓	✓	✓	✓	✓	✓	✓
assess adherence to treatment		✓	✓	✓	✓		✓*	✓
reassess diagnosis	✓	✓	✓*	✓	✓		✓*	
evaluate comorbidities	✓*	✓*		✓	✓		✓*	✓*
switch from antidepressants to NPT				✓	✓	✓		✓
consider neurostimulation				✓			✓	✓
check occurrence of side effects		✓	✓		✓			
consider substance abuse		✓*		✓			✓*	
increase appointments			✓					✓
consider longer periods for improvement							✓	
try previous treatments			✓					

CPG = Clinical Practice Guideline, MS = Ministerio de Salud, NICE = National Institute for Health and Care Excellence, ICSI= Institute for Clinical Systems Improvement, VA/DoD = US Department of Veterans Affairs (VA), US Department of Defense (DoD), APA-Psychology = American Psychological Association, CANMAT= Canadian Network for Mood and Anxiety Treatments, APA-Psychiatry= American Psychiatric Association, NPT = non-pharmacological treatment, * = not listed in the recommendations section but mentioned in the clinical practice guideline.

DISCUSSION

Although there are many modalities to treat depression, pharmacotherapy remains the most common first-line strategy.[12] However, clinical remission after treatment with first-line antidepressants is usually only achieved in a minority of patients.[14,67] Thus, in this review we compared the recommendations from the 8 (5 with AGREE's domain 3 score ≥ 80% and 3 most used/relevant in clinical practice) most relevant CPGs for the management of depression in adults who have shown an inadequate response to first-line antidepressant treatment.

Most CPGs agree on the need to reassess the diagnosis, assess the presence of comorbidities, assess adherence to treatment, adjust antidepressant dosage, and add psychotherapy as the first steps for those not responding to first line antidepressant treatment. However, our findings revealed important flaws in recommendations including not presenting a standardized definition of an adequate/inadequate/partial response; not establishing the length of treatment time needed to declare an inadequate/partial response/non-response; all CPGs include the possibility of switching the antidepressant, augmentation with other medicines and combination of antidepressants, but three CPGs do not recommend a clear sequence among them.

Convergencies among CPGs

Considering the first steps for inadequate response to first-line antidepressant treatment, reassessing the diagnosis is almost always one of the first steps. CPGs recommend the investigation of bipolarity, personality disorders and the presence of comorbidities. Assessing the adherence to treatment is also frequently included among the first steps. Some CPGs are constructed based on other CPGs and their

recommendations are identical in various aspects. In this regard, the Colombian guideline[25] place the assessment of adherence as the first step for patients with an inadequate response to treatment as does its font CPG, the NICE[26]. Increase of dose, another frequent recommendation curiously does not have consistent support by literature. It has been suggested that an increase in the dosage of most antidepressants may be effective for some patients, partially determined by individual differences in metabolizing enzymes, but not for others.[26] All CPGs include the possibilities of switching and adding another medicine, and most of them recommended switching to another antidepressant before combining or augmentation strategies (Table 2). Another convergence by most CPGs is the inclusion of antipsychotics, lithium and T3 as augmentation strategies to antidepressant tretament.[21–23,25–27] Adding psychotherapy to the antidepressant treatment is recommended by all, except the MS Chile guideline [24.] This strategy may decrease treatment abandonment, improve adherence to pharmacotherapy and increase the effectiveness of treatment.[68,69]

Divergencies and Shortcomings of CPGs

Among the shortcoming of CPGs, this review reveals a high heterogeneity in quality of the rigor of development (domain 3 of AGREE). A difficult to explain finding. The Diagnostic and Statistical Manual of Mental Disorders (DSM) V replaced DSM IV in 2013, and the diagnostic criteria for depressive disorder have been updated. Such change could impact on case identification and estimative of depression prevalence. However, diagnostic criteria are not covered by AGREE II checklist and differences in quality among CPGs might have not been influenced by that change in DSM version. CPGs were from distinct years, and the APA-Psychiatry, published in 2010, the oldest included CPG, received the worst score on quality of rigor in development. It is possible

that for the APA-Psychiatry and other CPGs the absence of a more recently updated version could have contributed to their low appraisal by AGREE-II.

Of concern, standardized definition of an inadequate/adequate/partial response is not clear in 3 CPGs. This is a problematic point considering that we selected most relevant CPGs.[12] The absence of a clear definition of such a central aspect limits the applicability of the recommendations, increasing the risk of a more severe course of depression and, potentially, suicide.[70] MacQueen *et al.*,[12] using the AGREE II, also found a lack of definition for inadequate response to antidepressant treatment in their review of 21 CPGs for treatment of depression published between 1980 and 2015.

For patients with inadequate or partial response, all CPGs include the possibilities of switching and adding another medicine. Although all CPGs recommend switching antidepressants for an inadequate antidepressant response, there is little scientific evidence supporting this approach.[71] Five CPGs recommend switching to another antidepressant before combining or augmentation strategies[21,24,26,27,28]. However, most CPGs do not specify whether switching should be made within the same or to a different antidepressant class. Here we have a specific difference in the CANMAT guideline[21], the recommendation is first switch to a more efficacious antidepressant, then to combination or augmentation e then switch to a second- or third-line antidepressant. CPGs are not consensual regarding the use of the terms combination and augmentation. The concept of augmentation to denominate the addition of a non-antidepressant medicine to the antidepressant and the term combination to designate the use of two antidepressants are not adopted by all CPGs.[26] The CANMAT[21] guideline, uses the term "adjunctive treatment" to denominate combination for two antidepressants or augmentation with other medicine; the APA-Psychology use the denomination "augment" to the use of two antidepressant. Also, the APA-Psychology guideline[28] suggests the possibility of the use

of two antidepressants but does not include the possibility of augmentation with other medicines. Most CPGs do not give the reader a clue of which could be tried first, augmentation or combination, only the ICSI CPG[27] establishes a sequency, recommending that drug combination should be first and then augmentation.

Other relevant point of variations is whether the CPGs recommend a class of antidepressant or specific drugs. For example, the CANMAT[21] guideline brings specific antidepressants and other specific drugs to be used as adjunctive medicine, drugs that are not recommended and also describes the criteria for the physician to decide on the drug substitution and adjunctive treatment, including the patients' preference.[21] On the other hand, other CPGs as the APA-Psychiatry guideline[22] did not mention specific antidepressants in detail in its recommendations. It should be considered that discrepancies of choices of particular strategies or medications found in our review may be governed by local contracting, availability or cost issues besides evidence-to-decision (EtD) frameworks as it is recommended[10].

Although most CPGs are congruent with the inclusion of antipsychotics, lithium and T3 as augmentation strategies to antidepressant treatment they usually do not stablish the sequency among them.[21–23,25–27]

Shortcomings and Strengths of our review

Our review has some limitations to be considered. It only included papers written in English, Portuguese, or Spanish. CPGs' recommendations were usually described in a specific section, but in some CPGs', recommendations are also found throughout the text making it difficult to ensure that we could capture all of them. To minimize this problem, we included the content of the recommendation's section and also conducted a comprehensive search in the CPGs for additional recommendations. Another limitation to be considered is the questionable quality of evidence of primary efficacy studies for

various therapeutic approaches, thus, weakness and disagreement among CPGs may at least in part reflect that condition. Last, we focus in some aspects, but the list of disagreements among the CPGs is long and there might be important points that we did not discuss here.

Strength points in this review are the use of the AGREE II to select CPGs with high-quality; the inclusion of 3 extra CPGs among the most relevant in clinical practice [21,22] and the selection and extraction of the data performed by two independent researchers. Additionally, convergencies and divergencies among CPGs identified in our study may offer an opportunity to practitioners review their practice and help institutions in the development and adaptation of a CPG for treatment of depression.

Final considerations

It's relevant to point out that discrepancies among CPGs have led health professionals to be hesitant in applying CPGs in clinical practice.[72] Improvement in quality will help healthcare professionals in the implementation of CPGs.[73] Acceptancy by clinicians is the key for CPGs[74] effective implementation and achievement of optimal patient care. Healthcare professionals have a limited time to read a reliable literature and CPGs are essential for decision making, our study shows topics that could be reviewed and improved.[72,75]

CONCLUSION

In conclusion, most CPGs for the treatment of depression converge in including checking adherence to treatment, reassessing diagnosis, evaluating comorbidities, changing antidepressant dosage an including psychotherapy as first steps for non-responsive to first line antidepressant patients. Switching antidepressants, augmentation/combining medicines are also included strategies. However, some

limitations are also present in most relevant CPGs for treatment of depression. The CPGs for the treatment of depression present differences in specific recommendations for non-responsive patients, mainly in their recommended strategic sequence. Additionally, some do not present a standardized definition of adequate/partial/inadequate response and differ with respect to the duration of treatment needed to declare that a patient did not respond to the treatment. Our opinion is that these topics deserve further consideration in future CPGs.

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Contributors

FCG, DOM, and ATS planned and developed the literature search strategy. IBS and FCG conducted the literature search. FCG and GCHFM realized the literature review. FCG, DOM, ATS, RF, ER, and IBS planned and developed the methodology. FCG, DOM, ATS, RF and ER conducted the data analysis. FCG, DOM, ATS, RF and ER interpreted the data. FCG, DOM, GCHFM, ATS, AFO, RF, ER, and IBS wrote the draft and final version of the manuscript. DOM, ATS, AFO, RF, ER, and IBS reviewed the manuscript. FCG, GCHFM and IBS. appraised the CPGs. All authors approved the final manuscript.

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Data supporting these study findings are openly available.

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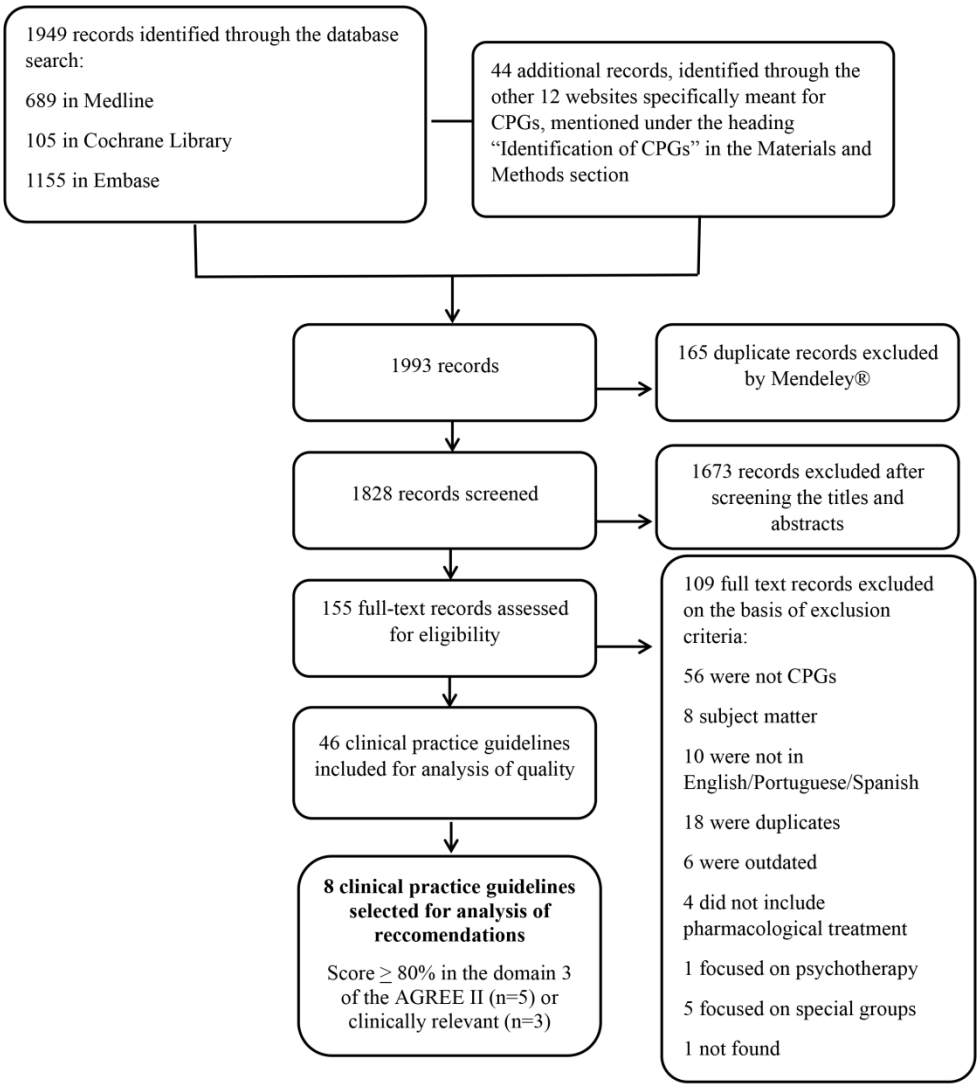
Figure 1

Flowchart of clinical practice guidelines selection



Flowchart of clinical practice guidelines selection

Appendix 1. Systematic search strategies

Medline (PubMed website)

{{{"Guideline"[Publication Type] OR Guideline as Topic"[Mesh] OR 'Practice Guideline"[Publication Type] OR 'Health Planes Guidelines'[Mesh]} OR 'Clinical Protocols'[Mesh]}} OR {'Consensus Development Conference, NIH" [Publication Type] OR {'Consensus Development Conference, NIH" [Publication Type] OR {'Consensus"[Mesh]}}} OR Standard of Care[Mesh] " Guideline" Publication Type] OR 'Guideline as Topic'[Mesh] OR 'Practice Guideline"[Publication Type] OR 'Health Planes Guidelines'[Mesh]} OR 'Clinical Protocols'[Mesh]}} OR {'Consensus Development Conference, NIH" [Publication Type] OR {'Consensus Development Conference, NIH" [Publication Type] OR {'Consensus"[Mesh]}}} OR Standard of Care[Mesh]}}} AND {{Depressive Disorder [Mesh] AND Depressive Disorder, Major [Mesh] OR Depressive Disorders OR disorder, Depressive OR Disorders, Depressive OR Neurosis, Depressives OR Depressive Neuroses OR Depressive Neurosis OR Neuroses, Depressive OR Depressions, Endogenous OR Endogenous Depression OR Endogenous Depressions OR Depressive Syndrome OR Depressive Syndromes OR Syndrome, Depressive OR Syndromes, Depressive OR depression, Neurotic OR Depressions, Neurotic OR Neurotic depression OR Neurotic Depressions OR Melhancholia OR Melancholias OR Unipolar Depression OR Depression, Unipolar OR Depressions, Unipolar OR Unipolar Depressions}}}

Cochrane Library

# 1	MeSH descriptor:[Guideline] explode all trees
# 2	MeSH descriptor:[Consensus] explode all trees
# 3	MeSH descriptor:[Clinical Protocols] explode all trees
# 4	#1 OR #2 OR #3
# 5	MeSH descriptor:[Depression] explode all trees
#6	#4 AND #5

EMBASE

((practice guidel'ne/mj OR 'consensus development'/exp/mj OR 'clin'cal protocol'/mj AND ('depression'/exp) AND (2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py AND [embase]/lim)

Appendix 2. Reasons for excluding clinical practice guidelines

References of the excluded guidelines	Reasons for exclusion
Institute for Clinical Systems Improvement. Adult Depression in Primary Care. Bloomington, MN: ICSI; 2016.	Duplicate
Austin M-P, Highet N, The Expert Working Group. Mental Health Care in the Perinatal Period: Australian Clinical	Duplicate
Practice Guideline. Melbourne, Australia: Centre of Perinatal Excellence; 2017.	
Grinspun, D, Bajnok I, Rey M. Delirium, Dementia, and Depression in Older Adults: Assessment and Care. Toronto, Canada: Registered Nurses' Association of Ontario; 2016.	Duplicate
National Guideline Clearinghouse. Delirium, Dementia, and Depression in Older Adults: Assessment and Care. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2016. Available from: https://www.guideline.gov. Accessed January 19, 2017.	Duplicate
National Institute for Health and Care Excellence. Depression in Adults: Recognition and Management. 2009. Available from: https://www.nice.org.uk/guidance/cg90/evidence. Accessed June 30, 2017.	Duplicate
Boltz M (Ed.). Evidence-based Geriatric Nursing Protocols for Best Practice. New York, NY: Springer; 2012.	Duplicate
Depression. University of Michigan Health System. NGC:008672.	Duplicate
Álvarez Ariza M, Atienza Merino G, Ávila González MJ, et al. GPC sobre el Manejo de la Depresión en el Adulto. Madrid, Spain: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014.	Duplicate
National Guideline Clearinghouse. Depression (Singapore). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2012. Available from https://www.guideline.gov/summaries/summary/39324. Accessed October 19, 2016.	Duplicate
Austin M-P, Highet N, The Expert Working Group. Mental Health Care in the Perinatal Period: Australian Clinical Practice Guideline. Melbourne, Australia: Centre of Perinatal Excellence; 2017.	Duplicate

McDermott B, Baigent M, Chanen A, et al. Clinical Practice Guidelines: Depression in Adolescents and Young Adults. Melbourne, Australia: Agency for Healthcare Research and Quality; 2010.	Duplicate
Michigan Quality Improvement Consortium Guideline. Primary Care Diagnosis and Management of Adults with Depression. Detroit, MI: MQIC; 2018. Available from: http://mqic.org/guidelines.htm. Accessed October 19, 2016.	Duplicate
National Institute for Health and Clinical Excellence. Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care. Leicester, UK: British Psychological Society; 2005.	Duplicate
Michigan Quality Improvement Consortium Guideline. Primary Care Diagnosis and Management of Adults with Depression. Detroit, MI: MQIC; 2018. Available from: http://mqic.org/guidelines.htm. Accessed October 19, 2016.	Duplicate
Connolly KR, Thase ME. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs* 2011;71(1):43–64. doi:10.2165/11587620-000000000-00000.	Duplicate
National Institute for Health and Care Excellence. Common Mental Health Disorders. Identification and Pathways to Care. London, UK: NICE; 2011.	Without pharmacological treatment
Grinspun, D, Bajnok I, Rey M. Delirium, Dementia, and Depression in Older Adults: Assessment and Care. Toronto, Canada: Registered Nurses' Association of Ontario; 2016.	Duplicate
Joffres M, Jaramillo A, Dickinson J, et al. Recommendations on screening for depression in adults. *CMAJ* 2013;185(9):775–82. doi:10.1503/cmaj.130403.	Without pharmacological treatment
Boltz M (Ed.). Evidence-based Geriatric Nursing Protocols for Best Practice. New York, NY: Springer; 2012.	Duplicate
Patten SB. Updated CANMAT guidelines for treatment of major depressive disorder. *Can J Psychiatry* 2016; 61(9):504–5. doi:10.1177/0706743716660034.	Without pharmacological treatment
Rush AJ, Aaronson ST, Demyttenaere K. Difficult-to-treat depression: a clinical and research roadmap for when remission is elusive. *Aust N Z J Psychiatry* 2019;53(2):109–18. doi:10.1177/0004867418808585.	Without pharmacological treatment
Frye MA. Clinical practice: bipolar disorder--a focus on depression. *N Engl J Med* 2011;364(1):51–9.	Subject matter
Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* 2015;49(12):1087–206. doi:10.1177/0004867415617657.	Duplicated

Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *J Clin Oncol* 2014;32(15):1605–19. doi:10.1200/JCO.2013.52.4611.	Subject matter
American Medical Directors Association. Guideline Summary: Depression in the Long Term Care Setting. Columbia, MD: AMDA; 2011.	Subject matter
Joffres M, Jaramillo A, Dickinson J, et al. Recommendations on screening for depression in adults. *CMAJ* 2013;185(9):775–82. doi:10.1503/cmaj.130403.	Subject matter
Li M, Kennedy EB, Byrne N, et al. The management of depression in patients with cancer: a clinical practice guide. *J Oncol Pract* 2016;12(8):747–56. doi:10.1200/JOP.2016.011072.	Subject matter
Ostacher MJ, Tandon R, Suppes T. Florida best practice psychotherapeutic medication guidelines for adults with bipolar disorder: a novel, practical, patient-centered guide for clinicians. *J Clin Psychiatry* 2016;77(7):920–6. doi:10.4088/JCP.15cs09841. Available in:	Subject matter
http://www.embase.com/search/results?subaction=viewrecord &from=export&id=L611538719.	
Pfennig A, Bschor T, Falkai P, et al. The diagnosis and treatment of bipolar disorder: recommendations from the current S3 guideline. *Dtsch Arztebl Int* 110(6):92–100. doi:10.3238/arztebl.2013.0092.	Subject matter
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Alexopoulos GS. Pharmacotherapy for late-life depression. *J Clin Psychiatry* 2011;72(1):e04. doi:10.4088/JCP.7085tx2cj.	Not a CPG
Andreescu C, Reynolds CF III. Late-life depression: evidencebased treatment and promising new directions for research and clinical practice. *Psychiatr Clin North Am* 2011;34(2):335–55. doi:10.1016/j.psc.2011.02.005.	Not a CPG
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Bohra HM, Novak M. Depression in patients with chronic kidney disease. *CANNT J* 2015;25(3):34–8.	Not a CPG
Busch FN, Sandberg LS. Combined treatment of depression. *Psychiatr Clin North Am* 2012;35(1):165–79. doi:10.1016/j.psc.2011.10.002.	Not a CPG
Cohen A. The QOF, NICE, and depression. *Br J Gen Pract* 2011;61(590):549. doi:10.3399/bjgp11X593785.	Not a CPG
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Canadian Agency for Drugs and Technologies in Health. Diagnosing, Screening, and Monitoring Depression in the Elderly: A Review of Guidelines. Ottawa, ON: CADTH; 2015.	Not a CPG
Canadian Agency for Drugs and Technologies in Health.	Not a CPG

Antidepressants in Elderly Patients with Major and Minor Depression: A Review of Clinical Effectiveness and Guidelines. Ottawa, ON: CADTH; 2015.	
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Horgan D, Dodd S. Combination antidepressants—use by GPs and psychiatrists. *Aust Fam Physician* 2011;40(6):397–400.	Not a CPG
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Kurian BT, Grannemann B, Trivedi MH. Feasible evidencebased strategies to manage depression in primary care. *Curr Psychiatr Rep* 2012;14(4):370–5. doi:10.1007/s11920-0120290-y.	Not a CPG
Laux G. Update treatment of depression—S3 Guideline, internet-based psychotherapy, antidepressants and driving ability. *Nervenheilkunde* 2016;35(10):691–6. doi:10.1055/s-0037-1616433.	Not a CPG

Leadholm AKK, Rothschild AJ, Nolen WAet al. The treatment of psychotic depression: is there consensus among guidelines and psychiatrists? *J Affect Disord* 145(2): 214–20. doi:10.1016/j.jad.2012.07.036.	Not a CPG
Malhi G, Oakley-Browne M, Hay P. Clinical practice guidelines project (CPG project) overview. *Aust N Z J Psychiatr* 2015;49(Supp 1):30. doi:10.1177/0004867415578344.	Not a CPG
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Oldham J. Fine-tuning our treatment strategies. *J Psychiatr Pract* 2011;17(3):157. doi:10.1097/01.pra.0000398408.13750.8d.	Not a CPG
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meeting the needs of clinicians? *Aust N Z J Psychiatry* 2016;50(10):1015–6. doi:10.1177/0004867416667828.	
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Reisdorf S. Revision of the national health care guidelines on unipolar depression. *Med Monatss Pharm* 2016;39(4):171–2.	Not a CPG

Roberge P, Fournier L, Brouillet H, et al. A provincial adaptation of clinical practice guidelines for depression in primary care: a case illustration of the ADAPTE method. *J Eval Clin Pract* 2015;21(6):1190–8. doi:10.1111/jep.12404.	Not a CPG
Schuklenk U, Vathorst SVD. Treatment-resistant major depressive disorder and assisted dying. *J Med Ethics* 2015;41(8), 577–83. doi:10.1136/medethics-2014-102458.	Not a CPG
Schulte-Körne G, Krick K. In reply. *Dtsch Arztebl Int* 2014;111(18):330. doi:10.3238/arztebl.2014.0330c.	Not a CPG
Tomba E, Fava GA. Treatment selection in depression: the role of clinical judgment. *Psychiatr Clin North Am* 2012;35(1):87–98. doi:10.1016/j.psc.2011.11.003.	Not a CPG
Treuer T, Liu C-Y, Salazar G, et al. Use of antidepressants in the treatment of depression in Asia: guidelines, clinical evidence, and experience revisited. *Asia Pac Psychiatry* 2013;5(4):219–30. doi:10.1111/appy.12090.	Not a CPG
Tundo A, Calabrese JR, Proietti L, et al. Short-term antidepressant treatment of bipolar depression: are ISBD recommendations useful in clinical practice? *J Affect Disord* 2015;171:155–60. doi:10.1016/j.jad.2014.09.019.	Not a CPG
Van Avendonk M, van Weel-Baumgarten E, van der Weele G, et al. Summary of the Dutch College of General Practitioners' practice guideline "Depression". *Ned Tijdschr Geneeskd* 2012;156(38):A5101.	Not a CPG
Vinberg M, Levinsen MF, Kessing LV. Treatment-resistant depression is treatable. *Ugeskr Laeger* 2011;173(9):651–4.	Not a CPG
Wang HR, Bahk WM, Park YM, et al. Korean medication algorithm for depressive disorder: comparisons with other treatment guidelines. *Psychiatry Investig* 2014;11(1):1–11. doi:10.4306/pi.2014.11.1.1.	Not a CPG
Won E, Park SC, Han KM, et al. Evidence-based, pharmacological treatment guideline for depression in Korea, revised edition. *J Korean Med Sci* 2014;29(4):468–84. doi:10.3346/jkms.2014.29.4.468.	Not a CPG
Xiang YT, Hu C, Wang G, et al. Prescribing patterns of antidepressants, antipsychotics and mood stabilizers in bipolar patients misdiagnosed with major depressive disorder in China. *Hum Psychopharmacol* 2012;27(6):626–31. doi:10.1002/hup.2262.	Not a CPG
Yang J, Han C, Yoon HK, et al. Experiences and barriers to implementation of clinical practice guideline for depression in Korea. *BMC Psychiatry* 2013;13:150. doi:10.1186/1471244X-13-150.	Not a CPG

Zimmerman M. Symptom severity and guideline-based treatment recommendations for depressed patients: implications of DSM-5's potential recommendation of the PHQ-9 as the measure of choice for depression severity. *Psychother Psychosom* 2012;81(6):329–32. doi:10.1159/000342262.	Not a CPG
Zimmerman M, Martinez JH, Friedman M, et al. How can we use depression severity to guide treatment selection when measures of depression categorize patients differently? *J Clin Psychiatry* 2012;73(10):1287–91. doi:10.4088/JCP.12m07775.	Not a CPG
Malhi GS, Outhred T, Hamilton A, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Med J Aust* 2018;208(4):175–80. doi:10.5694/mja17.00659.	Not a CPG
Evidence-Based Clinical Practice Guidelines for Depression in Adults on Traditional Korean Medicine; 2016.	Not found
S3-Leitlinie/Nationale Versorgungs Leitlinie Unipolare Depression; 2015. In German.	Language
Depression. Adapted Evidence-based Guideline. Ucrania; 2014 - Депресія. Адаптованаклінічнанастанова. In Ukrainian.	Language
[*Depressive Disorder. Depressie* (M44)]; 2012. In Dutch.	Language
Herrmann M, Gensichen J. Guidelines in general practice: the example depression. *Psychiatrie* 2015;66:119–24.	Language
Kuroki T, Tanaka T. [Threshold of application of antidepressant drugs for treatment of depressive disorder]. *Seishin Shinkeigaku Zasshi* 2015;117(4):269–76. In Japanese.	Language
Semba J. [Proper use of novel antidepressants in psychiatric clinical practice]. *Seishin Shinkeigaku Zasshi*. 2014;116(2):138–143. In Japanese.	Language
Yamada K. [Evidence of treatment for depressive episodes of bipolar disorder]. *Seishin Shinkeigaku Zasshi* 2011;113(9):873–9. In Japanese.	Language
Siu AL, US Preventive Services Task Force (USPSTF). Screening for depression in adults: US Preventive Services Task Force recommendation statement. *JAMA* 2016;315(4):380–7. doi:10.1001/jama.2015.18392.	Language
Thase ME. Recommendations for screening for depression in adults. *JAMA* 2016;315(4):349–50. doi:10.1001/jama.2015.18406.	Language

Patejuk-Mazurek I. Selected antidepressants and anxiolytics: practical guidelines and case studies. *Psychiatria* 2017;14(3):135–42.	Language
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6 (although not an explicit PICO)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	CRD42016043364
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 Appendix 2 9-10-11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22-23-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	25-26

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	26-27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	27-28

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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