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Factors associated with higher quality of clinical practice guidelines and their recommendations for the pharmacological treatment of depression: a systematic review

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ABSTRACT

Objective The objective of this study was to assess the quality of clinical practice guidelines (CPGs) for the pharmacological treatment of depression along with their recommendations and factors associated with higher quality.

Design We conducted a systematic review that included CPGs for the pharmacological treatment of depression in adults.

Data sources We searched for publications from 1 January 2011 to 31 December 2021, in MEDLINE, Cochrane Library, Embase, PsycINFO, BVS and 12 other databases and guideline repositories.

Eligibility criteria for selecting studies We included CPGs containing recommendations for the pharmacological treatment of depression in adults at outpatient care setting, regardless of whether it met the U.S. National Academy of Medicine criteria, or not. If a CPG included recommendations for both children and adults, they were considered. No language restriction was applied.

Data extraction and synthesis Data extraction was also conducted independently and in duplicate, a process that was validated in a previous project. The quality of the CPGs and their recommendations were assessed by three independent reviewers using Appraisal of Guidelines for Research and Evaluation (AGREE II) and Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence (AGREE-REX). A CPG was considered to be of high quality if AGREE II Domain 3 was ≥60%; while their recommendations were considered high if AGREE-REX Domain 1 was ≥60%.

Results Seventeen out of 63 (27%) CPGs were classified as high quality, while 7 (11.1%) had high-quality recommendations. The factors associated with higher-scoring CPGs and recommendations in the multiple linear regression analyses were 'Handling of conflicts of interest', 'Multiprofessional team' and 'Type of institution'. 'Inclusion of patient representative in the team' was also associated with higher-quality recommendations.

Conclusions The involvement of professionals from diverse backgrounds, the handling of conflicts of interest, and the inclusion of patients' perspectives should be prioritised by developers aiming for high-quality CPGs for the treatment of depression.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To increase the reliability of the quality assessment of the guidelines and recommendations, three reviewers independently conducted the assessment using both AGREE II and AGREE-REX evaluation tools. Before the assessment, the appraisers underwent rigorous training to ensure consistency in their evaluations.
⇒ The study was based on a comprehensive literature search on the pharmacological treatment of depression conducted in 17 databases using a sensitive strategy.
⇒ The inclusion of studies published in different languages made it difficult to include all documents present on the websites of specific institutions.

INTRODUCTION

Depression is a serious mental health problem that causes severe professional, economic, social and personal incapacitation.[1 2] The Global Burden of Disease Study 2017 estimated that more than 264 million people worldwide were affected by depression.[3] Moreover, according to the WHO, approximately 800 000 cases of suicide per year are attributable to this disease.[4] The prevalence of depression has increased considerably in the last few years,[5 6] overloading healthcare systems.[7] The COVID-19 pandemic increased

the prevalence of mental illness even further, generating an extra need of resources to overcome the burden of mental health disorders.[8] While a growing number of depression cases are being recognised and treated, rates of poor outcomes at 1 year in community populations remain high.[9] The optimisation of health resources for the treatment of depression by implementing evidence-based health interventions is challenging,[10] but necessary. In this scenario, adherence to high-quality clinical practice guidelines (CPGs) is vital.

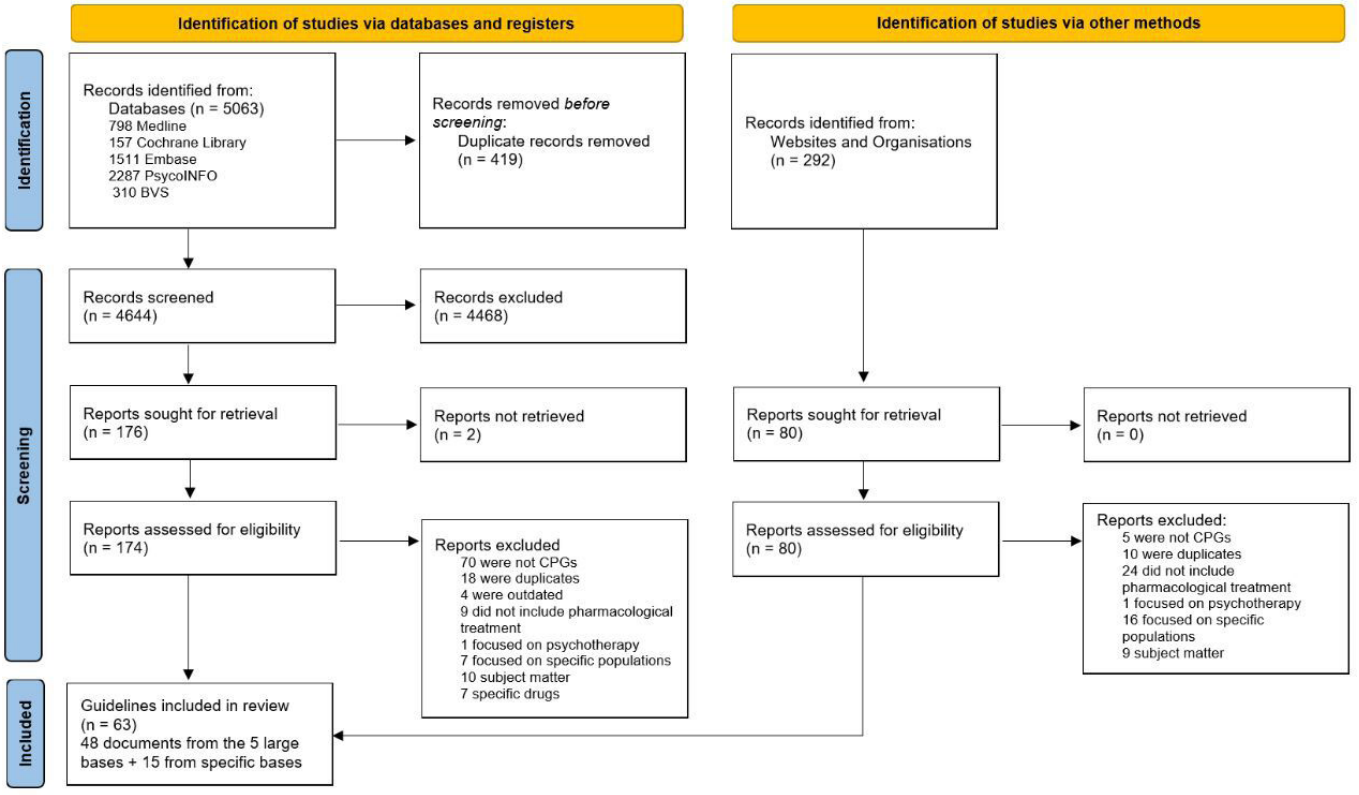
CPGs are documents that contain recommendations for the optimisation of patient care, developed through the systematic review of evidence and analysis of the risks, benefits and costs of interventions for each clinical health condition.[11] However, the potential benefits of a CPG depend on its quality. Only high-quality CPGs have the potential of facilitating expected positive outcomes in care of patients with depression, facilitating the clinical decision-making process, enhancing the education process of patients and professionals on the best practices, reducing unnecessary clinical variability, and improving the cost-effectiveness of healthcare.[12]

Nevertheless, there are some challenges associated with high-quality CPGs. The development of rigorous CPGs is a time-consuming and expensive task. High-quality CPGs need to be supported by systematic reviews which require significant time, effort and technical capacity to complete.[11] Guidelines need to be developed by a multiprofessional, independent team of experts that do not have competing interests. They also need to be continuously updated in response to new and relevant evidence, their development should be transparent and reproducible, and they need to consider patients' values and preferences.[11 13] Furthermore, the final documents of the guidelines need to be clear, well-organised and user-friendly.[12 14]

With the aim of providing support to guideline developers and users, some instruments have been developed to evaluate CPG quality. The most used tool for this purpose is the Appraisal of Guidelines for Research and Evaluation (AGREE II).[13 15 16] AGREE II has been validated and translated into several languages and provides online training and a clearly written user manual. This popular instrument enables a broad CPG quality assessment,[17] however it does not consider the quality of its recommendations.

To address this knowledge gap, the AGREE team developed an evidence-based AGREE II add-on, called the Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence (AGREE-REX), which enables the critical assessment of the recommendations of CPGs by their developers and users.[18–20] It is important

Figure legend



Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Br Med J*. 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

Figure 1 Flowchart of clinical practice guidelines (CPG) selection.

Table 1 Characteristics of the included clinical practice guidelines (CPGs)

Characteristic, no. (%)	n=63
Handling of conflicts of interest	11 (17.5)
Multiprofessional team	23 (36.5)
Inclusion of patient representative in the team	6 (9.5)
Governmental funding	24 (38.1)
Type of institution or organisation	
Independent researcher/University	19 (30.2)
Professional society	25 (39.7)
Governmental	19 (30.2)
Year of publication	
2011 to 2015	27 (42.9)
2016 to 2021	36 (57.1)

to note that AGREE-REX assesses the clinical credibility of the recommendations, meaning that it checks whether the recommendations have covered the key elements that make them more applicable to a particular context.[17] AGREE-REX considers that for a recommendation to be both high-quality and reliable, it must consider the values of the CPG developers and policy makers, in addition to patient preferences, and additional factors such as the clinical applicability and purpose of the CPG.[18] AGREE-REX complements the AGREE II evaluation by providing an evaluation of key elements that underpin the development of the recommendations. Therefore, for a complete evaluation of CPG quality, it is important to appraise both the general quality of the CPGs and its recommendations' quality.

Table 2 Clinical practice guidelines (CPGs) descriptive statistics for AGREE II and AGREE-REX Scores, n=63

Instrument domain	Mean±SD	Median (IQR)
AGREE II		
Scope and purpose	62.4±19.4	63 (46–78)
Stakeholder involvement	40.9±23.4	39 (22–59)
Rigour of development	39.4±26.4	35 (14–63)
Clarity of presentation	68.4±18.5	70 (57–83)
Applicability	29.3±21.3	23 (13–39)
Editorial independence	50.0±24.5	53 (33–72)
AGREE-REX		
Clinical applicability	36.3±19.2	35 (19–50)
Values and preferences	17.7±14.0	14 (7–25)
Implementability	35.1±15.7	33 (25–44)

The CPGs included were published between 1 January 2011 and 31 January 2021.
AGREE II, Appraisal of Guidelines for Research and Evaluation; AGREE-REX, Appraisal of Guidelines for Research and Evaluation-Recommendations Excellence; SD, standard deviation.

Some studies have already assessed the quality of CPGs for the pharmacological treatment of depression using AGREE II. However, the main focus of these studies was not on the quality of the documents or the factors related to high-quality. Furthermore, patient characteristics were either more restricted or included other chronic conditions, which did not specifically address depression.[21] To our knowledge, no study has assessed the quality of recommendations for the pharmacological treatment of depression using AGREE-REX.

By identifying the factors associated with high-quality CPG recommendations for the pharmacological treatment of depression, we can evaluate the areas for improvement that can help developers enhance their processes and create superior quality CPGs and recommendations. Therefore, our study aimed to assess the quality of CPGs for the treatment of depression and their recommendations and identify the factors associated with higher quality.

METHODS

The methods for this systematic review have already been previously reported in our published protocol[22] and are only briefly described here. Our methodology involved: (1) The identification of CPGs, (2) Extraction of CPGs' characteristics, (3) Appraisal of CPGs' quality using AGREE II, (4) Appraisal of the quality of CPG recommendations with AGREE-REX, and (5) Analysis of factors associated with the quality of CPGs and their recommendations.

The identification and appraisal of CPGs was initially conducted to elaborate a comparison of high-quality recommendations for the pharmacological treatment of depression. As a post hoc analysis, we then explored the factors associated with high-quality guidelines and recommendations.

We searched for publications from 1 January 2011 to 31 December 2021, in MEDLINE, Cochrane Library, Embase, PsycINFO, BVS (Virtual Health Library Regional Portal) and 12 other databases and guideline repositories (online supplemental material). The obtained citations were screened to select potentially eligible articles, which were obtained as full texts and reviewed to assess inclusion. Both previous steps were performed independently and in duplicate. Data extraction was also conducted independently and in duplicate, a process that was validated in a previous project.[21–23]

The quality of the CPGs was appraised by a team of multidisciplinary researchers trained according to a previously published protocol.[22] A final consolidated score ranging from 0% to 100% was obtained per AGREE II and AGREE-REX domains. More information on the methodology is provided in the published protocol.[22] Data were summarised by standard statistical methods and analysed using simple and multiple linear regression. Data were processed and analysed with IBM SPSS v.25.0. The detailed methodology is outlined in in online

Table 3 Contribution of CPG characteristics to AGREE II Domain 3 and AGREE-REX Domain 1 Scores (n=63)

	Univariate analysis			Multivariable analysis		
Characteristics	B	95% CI	P value	B	95% CI	P value
AGREE II Domain 3						
Handling of conflicts of interest	43.2	29.2 to 57.2	<0.001	20.4	7.9 to 32.9	0.002
Multiprofessional team	41.1	31.7 to 50.4	<0.001	22.2	10.2 to 34.2	<0.001
Inclusion of patient representative in the team	36.8	15.7 to 57.8	0.001	3.7	−11.5 to 18.9	0.627
Governmental funding	20.2	7.3 to 33.1	0.003	0.3	−12.5 to 13.1	0.964
Type of institution						
Independent researcher/university	Ref.	–	–	Ref.	–	–
Professional society	31.1	18.5 to 43.7	<0.001	17.8	7.6 to 27.9	0.001
Governmental	42.2	28.7 to 55.6	<0.001	19.8	4.5 to 35.1	0.012
Publication year >2015	−3.3	−16.9 to 10.4	0.631	0.5	−7.6 to 8.7	0.898
AGREE-REX Domain 1						
Handling of conflicts of interest	30.0	19.7 to 40.3	<0.001	12.8	3.4 to 22.2	0.008
Multiprofessional team	27.0	19.6 to 34.5	<0.001	11.2	2.2 to 20.3	0.016
Inclusion of patient representative in the team	31.3	16.7 to 45.9	<0.001	11.1	−0.3 to 22.6	0.056
Governmental funding	11.9	2.4 to 21.5	0.016	1.0	−8.7 to 10.6	0.841
Type of institution						
Independent researcher/university	Ref.	–	–	Ref.	–	–
Professional society	25.4	16.4 to 34.4	<0.001	17.0	9.4 to 24.6	<0.001
Governmental	29.1	19.5 to 38.7	<0.001	15.2	3.7 to 26.7	0.010
Publication year >2015	−1.6	−11.5 to 8.2	0.740	1.0	−5.2 to 7.1	0.748

AGREE II, Appraisal of Guidelines for Research & Evaluation; Domain 3, Rigour of Development; AGREE-REX, AGREE Recommendations Excellence; Domain 1, Clinical Applicability; B, linear regression coefficient representing the variable absolute impact (ie, increase or decrease) on the score; CI, confidence interval; P value, statistical significance.

supplemental material 1, while the reasons for excluding CPGs are shown in online supplemental material 2.

Patient and public involvement

No patient was involved.

RESULTS

CPG identification

We retrieved 5063 documents from the search and removed 419 duplicates; thus, we screened 4644 references. We discarded non-relevant references and retrieved 174 full texts to check their eligibility (two full texts could not be retrieved). A total of 126 documents were excluded and 48 documents were included after the full-text review. Moreover, we identified 15 documents from the guidelines' repositories. Ultimately, 63 CPGs were included in this study (see figure 1).

Characteristics of CPGs

Table 1 provides a summary of the characteristics of the included CPGs. Most were published after 2015 (36, 57.1%), 11 (17.5%) reported how conflicts of interest were handled and only 6 (9.5%) included patient representatives in the development team.

Appraisal of the quality of the guidelines and their recommendations

Table 2 presents descriptive statistics for the AGREE II and AGREE-REX Scores. Among the 63 CPGs, domains with low mean scores on the AGREE II (≤50%) were 'Stakeholder Involvement', 'Rigour of Development' and 'Applicability', while for the AGREE-REX, the mean scores in all domains were below 50%. The results of the appraisal of the CPGs' domains using the AGREE II and AGREE-REX are shown in table 1 in the online supplemental material 3. Table 3 presents the contribution of CPG characteristics to AGREE II Domain 3 and AGREE-REX Domain 1 scores.

Seventeen (27.0%) CPGs were classified as high quality according to AGREE II (Domain 3, Rigour of Development ≥60%).[24–40] Moreover, seven (11.1%) CPGs were also considered to have high-quality recommendations (AGREE-REX Domain 1, Clinical Applicability ≥60%).[24–31] All CPGs classified as being of high quality by AGREE-REX were also considered high quality according to AGREE II (online supplemental material).

Factors associated with higher quality

In the univariate analyses, all factors except publication year >2015 were found to have statistically significant

associations with AGREE II Domain 3 and AGREE-REX Domain 1. For AGREE II Domain 3, the multiple linear regression analysis showed that 'Handling of conflicts of interest', 'Multiprofessional team' and 'Type of institution' were statistically significant factors associated with increased scores. Regarding 'Type of institution', both 'Professional society' and 'Governmental institutions' presented higher scores when compared with 'Independent researcher/University'. The remaining factors (ie, 'Inclusion of patient representative in the team', 'Governmental funding' and 'Publication yr.>2015') did not reach statistical significance.

When considering AGREE-REX Domain 1, the same three factors were deemed to have a significant association with higher scores in the multiple linear regression model: 'Handling of conflicts of interest', 'Multiprofessional team' and 'Type of institution'. Similarly, for AGREE-REX Domain 1, institutions represented by 'Independent researcher/University' were those found to have lower scores when compared with 'Professional society' and 'Governmental institutions'. However, it is important to note that 'Inclusion of patient representative in the team' reached borderline statistical significance (p=0.056) and was associated with higher AGREE-REX Domain 1 scores.

DISCUSSION

In this systematic review, we identified 63 CPGs for the treatment of depression in adults. We found that few guidelines were classified as high quality according to AGREE II (17/63, 27.0%) and even fewer were considered to have high-quality recommendations according to AGREE-REX (7/63, 11.1%). The factors associated with higher-scoring CPGs (AGREE II Domain 3) and recommendations (AGREE-REX Domain 1) in our multiple linear regression analyses were 'Handling of conflicts of interest', 'Multiprofessional team' and 'Type of institution', with 'Professional society' and 'Governmental institutions' presenting higher scores when compared with 'Independent researcher/University'. Additionally, 'Inclusion of patient representative in the team' was found to have borderline statistical significance (p=0.056) with higher AGREE-REX Domain 1 Scores, which are related to improved clinical applicability.

In the multivariable analysis, 'Inclusion of patient representative in the team' was no longer significant in the model analysing AGREE II Domain 3 (Rigour of Development). This finding could be explained by the small number of CPGs with this particular characteristic declared, which may produce less reliable estimates and wide CIs in a more saturated model. In addition, 'Governmental funding' lost its statistical significance, probably because it may be a surrogate marker of the involvement of 'Governmental institutions'.

We identified several domains with suboptimal performance as evaluated with the AGREE II and AGREE-REX tools. With the AGREE II tool, the worst-scored domains were 'Applicability', 'Rigour of development' and 'Stakeholder involvement'. These findings show that CPGs may not always be based on the best evidence. Many currently available CPGs do not improve the quality of care for patients and may lead to the waste of scarce resources.[41–43] In other words, low scores in AGREE II Domain 3 (Rigour of Development) may indicate that most pharmacological treatments for depression did not report or perform the methodological processes expected for high-quality guidelines. Therefore, these CPGs had low or no use of appropriate development methods, selection and synthesis of evidence, and recommendations.

With the AGREE-REX tool, all three domains—'Clinical applicability', 'Values and preferences' and 'Implementability'—received low scores. The domain with the worst quality was 'Values', signalling that CPGs did not address the preferences of professionals, policy makers, developers or patient representatives in their recommendations. The values of policy makers are frequently missing, although some CPGs mention the term 'equity'—one of the values and preferences—as an important concept and as a factor considered in its development. Low scores in Domain 2 (Values) have also been found when applying AGREE-REX in CPGs for different health conditions.[20] Considering that therapeutic failure and adverse events in depression treatment are not uncommon, considering the values of patients, professionals, developers and policy/decision makers might be central to ensuring the effectiveness of a CPG.

In AGREE-REX Domain 1 (Clinical Applicability), we identified that the CPGs failed to clearly report the analysis of the quality of the studies, develop a list of relevant treatment outcomes (eg, quality of life, symptomatic remission, response) and appoint a patient representative as a team member. Finally, regarding AGREE-REX Domain 3 (Implementability), CPGs did not mention the anticipated impact when implementing recommendations and in the formal analysis of costs beyond the definitions of audit criteria to verify such implementation. Finally, low scores in AGREE II Domain 5 (Applicability) and AGREE-REX Domain 3 (Implementability) reveal a lack of consideration to implement strategies for clinical practice, which may lead to an ineffective interpretation of the best available evidence in practice.

We found that the handling of conflicts of interest was relevant in determining a high-quality status for a CPG and its recommendations. Such results call attention to previous reports supporting that simply declaring conflicts of interest is not enough.[44] Declaring potential conflicts of interests is not sufficient to avoid bias in the CPG development. Handling these conflicts by removing participants with conflicts from specific discussions, from voting or from the guideline group is essential to maintain rigour and transparency in the development process. The mean score of the 'Editorial independence' domain in AGREE II, the domain that includes how to handle conflicts of interest, was 50.0, contrasting with the mean scores of the highest-scored domains: 'Clarity of presentation' with

68.4 and 'Scope and purpose' with 62.4. This indicates a need for increasing attention to improve 'Handling of conflicts of interest' when developing a CPG.

We also found that a 'Multiprofessional team' was associated with higher quality in CPGs and their recommendations. These results may support the implementation of multiprofessional teams working together and sharing different practices and knowledge may offer improved results for patients, organisations and health systems.[45 46]

According to our analyses, 'Inclusion of patient representative in the team' may also be important for the quality of recommendations. Considering patients unique views, preferences and values regarding treatment benefits and harms enriches CPGs, helps minimise disease stigmatisation and improves adherence to treatment.[47–50]

A study by Zafra-Tanaka *et al*[51] analysed the quality and characteristics of 11 CPGs for depression published from January 2014 to May 2018 using the AGREE II instrument. Their findings revealed that <50% of these CPGs (5/11) have shared their search strategies or listed the studies used to develop the recommendations (4/11).[51] These information gaps make it more difficult to understand the possible biases such as potential conflicts of interest in the formulation of the recommendations provided in CPGs, thereby undermining health professionals' trust in these guidelines. Only 18% of the CPGs (2/11) have included patient representatives in their development team. Another relevant finding of this study was that only 27% (3/11) of the CPGs had a score of ≥70% in AGREE II Domain 3 (methodological rigour).

In addition, in a systematic review conducted by our group, the Chronic Diseases and Informed Decisions Research Group (CHRONIDE),[21] the methodological rigour was evaluated using AGREE II for 421 CPGs for treating chronic non-communicable diseases (including depression) in primary healthcare, <25% of those CPGs (99/421) were considered as having high quality. Of all the CPGs evaluated in the study, 31 CPGs were for treating depression. Of these, only 45% (14/31) were considered high quality (≥60% in AGREE II Domain 3). Remarkably, no associations between geographical region and quality of CPGs were found, unlike the findings of other studies.[52 53] Inclusion of >20 authors, being developed by government institutions and disclosure of financing support were associated with a higher quality based on logistic regression analysis. The authors raised a point that the government institutions have more financial and human resources for developing CPGs, which is generally a lengthy and costly process. Moreover, the study also revealed that Domain 4 (Applicability) received lower scores in the AGREE II assessment, either for the CPGs to treat depression or for the CPGs as a whole.

The findings reported by Zafra-Tanaka *et al*[51] and Molino *et al*[21] (the CHRONIDE Group) demonstrate that professionals and policy makers should know that only few CPGs for adults with depression demonstrate high developmental rigour. In addition, the relevance of including the patient's viewpoints, highlighted by Zafra-Tanaka *et al*,[51] converges to low quality of applicability detected by Molino *et al*.[21] Thus, the findings indicate that healthcare policy makers should invest in improving the developmental rigour of CPGs to attain the confidence of professionals using them and, on the implementation, and monitoring of recommendations to ensure their applicability. Following these principles, the role of CPGs as a tool to promote evidence-based health is safeguarded.

This article has several strengths. First, we conducted a comprehensive search across 17 CPG databases and repositories. To ensure a comprehensive quality assessment of the guidelines and recommendations, three independent raters were trained rigorously and used both AGREE II and AGREE-REX evaluation tools. This contributed to increase the reliability of quality assessment. Moreover, the use of AGREE-REX is still incipient and at the time of writing fewer than 10 studies have used this tool for the appraisal of the quality of CPGs recommendations.

Nevertheless, this study also has some limitations. To better evaluate the guidelines and their recommendations, whenever possible, we reviewed their supplemental materials and the methodological guidance of their institutions. However, the search for these documents was conducted in the organisations' websites, and we may have missed additional relevant documents that may impact the final evaluations. Moreover, the inclusion of studies published in different languages made it difficult to include all documents present on the websites of specific institutions.

Another aspect is that although most included CPGs were published after the release of The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) in 2013, some of them may have relied on DSM-IV definitions. However, since the evaluation of CPG quality does not specifically involve diagnostic criteria, it is unlikely that this could influence the results observed in this study.

Finally, as there were very few CPGs classified as high quality, we obtained wide CIs for the associations, which creates uncertainty regarding the estimates. Therefore, caution is recommended when interpreting our results. However, this possible limitation does not lessen the relevance of our work since, at least to our knowledge, this is the first study to assess the quality of recommendations of CPGs for the treatment of depression and to explore the factors associated with higher-quality CPGs and their recommendations.

CONCLUSION

We identified 63 CPGs for the pharmacological treatment of depression in adults, with 27.0% classified as high quality and 11.1% as having high-quality recommendations. The factors 'Handling of conflicts of interest', 'Multiprofessional team' and 'Type of institution' were significantly associated with higher quality in AGREE II Domain 3 and AGREE-REX Domain 1, followed by 'Inclusion of patient representative in the team', which may have an important role in AGREE-REX Domain 1.

CPG developers should be aware of the above characteristics to obtain more reliable and implementable recommendations. They should focus on improving quality as a whole and, more emphatically, on developing better recommendations rather than creating new ones with similar limitations.

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Supplemental Material 1 – Methods details

Theoretical rationale for choosing variables of interest to assess their association with the quality of CPGs and their recommendations

1) **Handling of conflicts of interest**: In order to have impartial and reliable recommendations, a CPG must not only declare conflicts but also have a handling of conflicts of interest policy. This policy is commonly achieved by editorial independence. Although we have not used in our analyses a variable directly related to the AGREE II domain "Editorial independence", we have assessed "Handling of conflicts of interest", which could be considered a proxy of this domain and is a fundamental characteristic for unbiased recommendations.[1]

2) **Multiprofessional team**: The development of high-quality CPGs is frequently associated with multidisciplinary teams in order to incorporate different knowledge and apply them in the recommendations. [1,2]

3) **Inclusion of patient representative in the team**: This characteristic usually occurs in clinical practice guidelines (CPGs) of higher methodological quality. In addition, interested party's participation (*i.e.*, patients) is fundamental to the development of acceptable recommendations (Guidelines International Network, 2020). [3]

4) **Governmental funding**: Government-funded teams are more likely to have a larger number of professionals involved and more resources allocated allowing a longer and thoroughly review. Developing high quality CPGs usually requires these resources. [1,4]

5) **Type of institution**: The type of institution was considered in the model since this variable has been mentioned by previous studies to be associated with higher scores on the AGREE II "rigour of development". [4]

6) **Publication year after 2015**: We hypothesized that newer CPGs and updated or revised versions tend to be associated with higher "rigour of development and highest quality" scores of the recommendations. [4]

Identifying and selecting CPGs

For the selection of published CPGs, we searched for documents published from January 1, 2011 to December 31, 2021. A period longer than 10 years was considered because some CPGs are not systematically updated. In the occurrence of two or more versions of the same guideline we included only the most recent updated version. The following databases were searched: MEDLINE (via PubMed), Cochrane Library, Embase, PsycINFO, and BVS. Additional searches were performed in the following websites: Australian Clinical Practice Guidelines, National Committee for Health Technology Incorporation (Brazilian Government), Canadian Agency for Drugs and Technologies in Health, Canadian Medical Association, Chilean Ministry of Health, Colombian Ministry of Health and Social Protection, Guidelines International Network, Institute for Clinical Systems Improvement, Portal Guía Salud, Scottish Intercollegiate Guidelines Network, and the National Institute for Health and Care Excellence, Guideline Central, ECRI library. Specific details related to the databases used in this study and the terms used in these repositories are shown below:

Medline (via PubMed)

((((("Guideline" [Publication Type] OR "CPGs as Topic"[Mesh] OR "Practice Guideline" [Publication Type] OR "Health Planning CPGs"[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 "CPGs as Topic"[Mesh] OR "Practice Guideline" [Publication Type] OR "Health Planning CPGs"[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))
Embase:
#1 'practice guideline'/mj OR 'consensus development'/exp/mj OR 'clinical protocol'/mj #2 'depression'/exp
#3 #1 AND #2

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

PsychINFO
((Any Field: (depression))) AND ((Any Field: (guideline)) OR (Any Field: (consensus)) OR (Any Field: ("clinical protocol"))) AND Year: 2011 To 9999
((Any Field: (depression))) AND ((Any Field: (guideline)) OR (Any Field: (consensus)) OR (Any Field: ("clinical protocol"))) AND Year: 2011 To 9999

BVS
((guideline) OR (consensus) OR (clinical protocol)) AND (depression) AND (db:("LILACS" OR "IBECS" OR "WHOLIS" OR "BDENF" OR "BINACIS" OR "INDEXPSI" OR "BIGG" OR "BBO" OR "CUMED")) AND (year_cluster:[2011 TO 2021])

We included documents between January 1, 2011, to December 31, 2021; containing recommendations for the pharmacological treatment of depression in adults at outpatient care setting, regardless of whether it met the U.S. National Academy of Medicine. If a CPG included recommendations for both children and adults, they were considered. No language restriction was applied; CPGs that were in languages other than Portuguese, English, or Spanish were translated into Portuguese by a professional translation service. We excluded CPGs for specific populations (e.g., treatment of pregnant women); local CPGs developed by hospitals or originations intended to be applied only at a local level and treatment of depression in comorbidity with specific diseases (e.g., depression in patients with diabetes).

Retrieved references were exported to the online platform Rayyan® reference manager. [5] After removal of duplicates, references were screened by two independent researchers. Then searched for the full texts, and these were reviewed in duplicate. Discrepancies between researchers were resolved by consensus. When no consensus was reached, a third evaluator was involved.

Extracting the characteristics of the CPGs

A Google Form was used for the extraction of general CPG data. The process of data extraction by two independent researchers was validated in a previous project [4] focused on osteoporosis CPGs conducted by our team. [6] We extracted the following independent variables: year of publication of the most recent version of the CPGs (2011 to 2014/2015 to 2021); type of institution (Governmental or University; Professional society), inclusion of a patient representative in the team (yes/no), multiprofessional team (yes - different professions/no - only one profession), governmental funding (yes/no), and policy for handling of conflicts of interest (yes/no). The type of institution classification and the funding variables were defined as governmental, even if the governmental institution had partnership with other types of institutions. These factors were selected because they are included in the AGREE II [7], AGREE-REX [8] and IOM. [9] Additionally, they are commonly found in literature articles [4,10] related to guideline's quality.

Appraisal of the CPGs quality

AGREE II is a reliable and validated tool composed by 23 items, clustered in six domains. The appraisal team comprised multidisciplinary researchers, including pharmacists, nurses, and public health professionals previously trained according to protocol. [11] The training consisted of reading the AGREE II manual. [7] Subsequently, the evaluators appraised the CPG quality on chronic pain [12], Gaucher disease [13], and for the treatment of obesity. [14] A discussion was held with previously trained evaluators on the evaluations made. In the next stage of training, the team appraised the most recent two CPGs for hyperthyroidism [15] and urinary tract infection. [16]

The appraisers assigned a score from 1 to 7 for each AGREE II item (following a 7point Likert scale). Each guideline was appraised by three appraisers as suggested by the AGREE Next Steps Consortium [7] using the AGREE-PLUS Platform. [17] A difference of two or more points in the individual items' [4,11,18] scores was considered discrepant and was resolved by consensus between the appraisers to obtain the final score. A final consolidated score was obtained from 0-100% per domain as suggested by the AGREE II Manual.

Appraisal of the quality of the recommendations of the CPGs

We used the AGREE-REX instrument to appraise the quality of the CPG recommendations. All recommendations were grouped and analysed for each CPG, according to one of the options recommended in the AGREE-REX manual. [8] AGREE-REX consists of nine items clustered into three domains: clinical applicability, values and preferences, and implementability. The same team of appraisers that assessed the quality of the CPGs using AGREE II also assessed the quality of the recommendations. The team was also trained for this evaluation. The three appraisers assigned a score from 1 to 7 for each item (following a 7-point Likert scale). When there was a discrepancy of two points or more, the evaluators discussed it until they reached consensus. A final consolidated score was obtained from 0-100% per AGREE-REX domain as suggested by the AGREE-REX Manual. [8] The scores of each evaluator were inserted in a Google Form®.

Statistical data analysis

Quantitative data were described using mean, standard deviation, median, and interquartile range. Categorical variables were presented as frequencies and percentages.

The CPGs were considered high-quality if they scored ≥60% in the AGREE II Rigour of Development domain, as it has been previously recommended. [4,10,19-22] The CPGs' recommendations were considered high-quality if they scored ≥60% in the AGREE-REX Clinical Applicability domain which considers the appropriateness of recommendations for clinical practice, patient needs, and the intended impact of guideline implementation.

Since the outcomes of high-quality CPGs and high-quality recommendations showed only 17 and 7 events, respectively, instead of analysing the binary characteristics we decided to model the scores directly. We used linear regression analysis and with this approach we were able to estimate the impact that each studied factor had on the AGREE II domain 3 and AGREE-REX domain 1 scores. The regression coefficients were obtained with a simple unadjusted model (univariate) and with an adjusted model (multivariable). Results with p values below 0.05 were deemed statistically significant. Data were processed and analyzed with IBM-SPSS version 25.0.

Supplemental material 2 – Reasons for excluding clinical practice guideline (CPG)

Reference of the excluded CPG	Reasons for exclusion
1. Institute for Clinical Systems Improvement. Adult Depression in Primary Care. Bloomington, MN: ICSI, 2016.	Duplicate
2. Grinspun, D, Bajnok I, Rey M. Delirium, Dementia, and Depression in Older Adults: Assessment and Care. Toronto, Canada: Registered 'urses' Association of Ontario, 2016.	Duplicate
3. Boltz M (Ed.). Evidence-based Geriatric Nursing Protocols for Best Practice. New York, NY: Springer, 2012.	Duplicate
4. MICHIGAN MEDICINE. Ambulatory unipolar depression guideline. [Ann Arbor]: UM; 2021. Available from: https://michmed-public.policystat.com/policy/8093108/latest/.	Duplicate
5. 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
6. National Guideline Clearinghouse. Depression (Singapore). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ), 2012. Available from: https://www.guideline.gov/summaries/summary/39324.	Duplicate
7. Management of Major Depressive Disorder Working Group. VA/DoD clinical practice guideline for the management of major depressive disor[de]r. 3rd ed. Washington, DC: US Department of Veterans Affairs, US Department of Defense, 2016.	Duplicate
8. 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.	Focused on specific populations
9. 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.	Focused on specific populations
10. 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. .	Duplicate
11. 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.	Focused on specific populations
12. 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
13. Kennedy SH, Lam RW, McIntyre RS, *et al.* Canadian network for mood and anxiety treatments (CANMAT), 2016, clinical CPGs for the management of adults with major depressive disorder: section 3: pharmacological treatments. *Can J Psychiatry*. 2016, 61(9)540-560. DOI: 10.1177/0706743716659417.	Duplicate

Reference of the excluded CPG	Reasons for exclusion
14. Taylor RW, Marwood L, Oprea E, *et al.* Pharmacological Augmentation in Unipolar Depression: A Guide to the Guidelines. Int J Neuropsychopharmacol. 2020, 23(9):587-625. DOI:10.1093/ijnp/pyaa033.	Duplicate
15. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strate2umaries2hiatrychiatr Dis Treat. 2020,16:221-234. Published 2020 Jan 21. DOI: 10.2147/NDT.S198774.	Duplicate
16. Samochowiec J, Dudek D, Kucharska Mazur J, Murawiec S, Rymaszewska J, Cubała WJ, Heitzman J, Szulc A, Bała M, Gałecki P. Pharmacological treatment of a depressive episode and recurrent depressive dis–rder - guidelines of the Polish Psychiatric Association and the National Consultant for Adult Psychiatry. Psychiatr Pol. 2021 Mar 12;55(2):235-259. English, Polish. DOI: 10.12740/PP/ OnlineFirst/132496. Epub 2021 Mar 12. PMID: 34365477.	Duplicate
17. MICHIGAN MEDICINE. Ambulatory unipolar depression guideline. [Ann Arbor]: UM; 2021. Available from: https://michmed-public.policystat.com/policy/8093108/latest/..	Duplicate
18. MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION. Management of major depressive disorder. 2nd ed. Putrajaya: MaHTAS, 2019. Available from: http://www.psychiatry-malaysia.org/...	Duplicate
19. Malhi GS, Bell E, Boyce P, Bassett D, Berk M, Bryant R, Gitlin M, Hamilton A, Hazell P, Hopwood M, Lyndon B, McIntyre RS, Morris G, Mulder R, Porter R, Singh AB, Yatham LN, Young A, Murray G. The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. Bipolar Disord. 2020 Dec, 22(8):805-821. DOI: 10.1111/bdi.13036. PMID: 33296123.	Subject matter
20. Moeller SB, Gbyl K, Hjorthøj C, Andreasen M, Austin SF, Buchholtz PE, Fønss L, Hjerrild S, Hogervorst L, Jørgensen MB, Ladegaard N, Martiny K, Meile J, Packness A, Sigaard KR, Straarup K, Straszek SPV, Soerensen CH, Welcher B, Videbech P. Treatment of difficult-to-treat depre–sion - clinical guideline for selected interventions. Nord J Psychiatry. 2022 Apr, 76(3):177-188. DOI: 10.1080/08039488.2021.1952303. Epub 2021 Aug 28. PMID: 34455900.	Duplicate
21. Kennedy SH, Lam RW, McIntyre RS, *et al.* Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. Can J Psychiatry 2016, 61:540-60.	Duplicate
22. National Institute for Health and Care Excellence. Depression in Adults: Recognition and Management. 2009. Available from: https://www.nice.org.uk/gui dance/cg90/evidence.	Duplicate

Reference of the excluded CPG	Reasons for exclusion
23. Ministerio de Salud (CL). Depresión em personas de 15 años y más. Santiago: Minsal, 2013.	Duplicate
24. Ministerio de Salud (COL). Detección temprana y diagnóstico del episodio depresivo y trastorno depresivo recurrente en adultos: atención integral de los adultos con diagnóstico de episódio depresivo o trastorno depresivo recurrente: Guía de práctica clínica. Bogotá: Minsalud; 2013 [cited 2017 Jun 30]. Available from: http://www.iets.org.co/reportes-iets/Documentacin%20. Reportes/Gu%C3%ADa. Completa. Depresion, 2013.pdf	Duplicate
25. 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
26. National Guideline Clearinghouse. Depression (Singapore). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2012. Available from: https://www.guideline.gov/ summaries/summary/39324..	Duplicate
27. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression- guideline.	Duplicate
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29. Bennabi D, Yrondi A, Charpeaud T, Genty JB, Destouches S, Lancrenon S, Allaili N, Bellivier F, Bougerol T, Camus V, Doumy O, Dorey JM, Haesebaert F, Holtzmann J, Lançon C, Lefebvre M, Moliere F, Nieto I, Rabu C, Richieri R, Schmitt L, Stephan F, Vaiva G, Walter M, Leboyer M, El-Hage W, Aouizerate B, Haffen E, Llorca PM, Courtet P. Clinical guidelines for the management of depression with specific comorbid psychiatric conditions French recommendations from experts (the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental). BMC Psychiatry. 2019 Jan 30, 19(1):50. DOI: 10.1186/s12888-019-2025-7. PMID: 30700272, PMCID: PMC6354367.	Duplicate
30. Malhi, G. S. *et al.* Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. Medical Journal of Australia, Sydney, v. 208, n. 5, 2018. DOI http://doi.org/ 10.5694/mja17.00659. Available from: https://www.mja.com. au/journal/2018/208/4/royal-australian-and-new-zealand-college-psychiatrists-clinical-practice.	Duplicate

Reference of the excluded CPG	Reasons for exclusion
31. Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians, 2016. https://www.acpjournals.org/doi/10.7326 /M15-2570.	Duplicate
32. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psycho. Available from: https://www.bap.org.uk/pdfs/BAP_ Guidelines-Antidepressants. pdf.pharmacologyguidelines. Journal of Psychopharmacology, 2015, v. 29(5) 459-525 DOI: 10.1177/0269881115581093 jop.sagepub.com.	Duplicate
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Supplemental Material 3 – Results

Table 1. Appraisal of CPGs for Research & Evaluation Instrument AGREE II domain scores (%) and AGREE-REX domain scores (%).

Country / Study	AGREE II domains' scores						AGREE-REX domains' scores		
	1. Scope and purpose	2. Stakeholder involvement	3. Rigour of development	4. Clarity of presentation	5. Applicability	6. Editorial independence	1. Clinical applicability	2. Values and preferences	3. Implementabilit
Chile, Ministerio de Salud [23]	83	76	89	94	57	17	33	29	41
Colombia, Ministerio de Salud [24]	100	85	86	100	96	92	72	57	67
United Kingdom, National Institute for Health and Care Excellence [25]	89	83	84	81	71	75	87	67	75
Germany, Härter et al. [26]	69	78	83	87	58	72	61	42	64
Peru EsSalud [27]	72	52	82	87	39	67	67	36	50
USA, Trangle et al. [28]	96	78	81	91	72	97	55	36	50
USA, American Psychological Association [29]	91	67	81	80	65	83	81	44	50
USA, Management of Major Depressive Disorder Working Group [30]	93	76	78	94	38	58	67	31	56
USA, Kaiser Permanente Care Management Institute [31]	83	63	76	93	46	58	54	25	33
Spain, García-Herrera Pérez Bryan et al. [32]	74	59	72	85	64	75	52	26	61
Spain, Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, Ministry of Health, Social Services and Equality [33]	94	93	70	91	75	53	67	36	67
Canada, Registered Nurses' Association of Ontario [34]	72	74	69	80	76	86	57	42	67
USA, Qaseem et al. [35]	80	39	69	70	32	67	48	11	33
Mexico, Instituto Mexicano del Seguro Social [36]	87	46	69	83	14	67	48	11	42
Mexico, Secretaría del Salud [37]	81	43	69	80	32	31	43	11	50
Mexico, Secretaría del Salud [38]	94	56	63	81	42	64	43	15	42
Singapore, Chua et al. [39]	78	72	60	89	50	28	59	19	44
Australia, Malhi et al. [40]	74	63	58	78	24	67	50	22	44

Country / Study	AGREE II domains' scores						AGREE-REX domains' scores		
	1. Scope and purpose	2. Stakeholder involvement	3. Rigour of development	4. Clarity of presentation	5. Applicability	6. Editorial independence	1. Clinical applicability	2. Values and preferences	3. Implementabilit
Michigan Ambulatory Unipolar Depression Guideline [41]	65	43	57	80	33	53	41	28	31
France, Driot et al. [42]	69	30	56	72	11	83	35	4	33
Several countries, Bauer et al. [43]	61	54	54	83	32	75	39	11	22
Canada, Kennedy et al. [44]	63	48	54	89	26	53	44	17	36
Several countries, Dua et al. [45]	69	74	50	74	29	75	41	25	47
USA, McIntyre et al. [46]	87	56	48	83	32	69	39	21	33
Several countries, Bauer et al. [47]	69	48	47	61	28	75	48	15	19
Malaysia, Malaysian Health Technology Assessment Section [48]	81	50	47	70	54	78	59	33	67
USA, Gelenberg et al. [49]	48	43	46	83	44	42	59	32	42
The Netherlands, Nederland Depressie [50]	70	70	42	65	22	50	28	19	33
United Kingdom, Cleare et al. [51]	67	57	40	69	13	58	52	22	33
Korea, Won et al. [52]	57	28	38	67	21	44	35	14	42
Finland, Suomalainen Lääkäriseura Duodecim [53]	50	61	36	65	40	56	44	21	50
USA, Ruberto et al. [54]	43	11	35	39	1	72	15	4	11
Canada, CPGs and Protocols Advisory Committee, Ministry of Health, British Columbia [55]	85	37	35	85	39	42	37	21	44
USA, Giakoumatos and Osser [56]	61	19	33	83	26	75	30	21	14
France, Bennabi et al. [57]	72	26	31	85	10	81	20	8	25
Saudi Arabia, Okasha et al. [58]	44	26	31	61	31	33	37	11	31
Several countries, Dodd S, Mitchell PB, Bauer et al. [59]	72	31	27	57	17	25	41	22	31
Several countries, Bauer et al. [60]	56	41	23	76	21	50	30	8	36
France, Bennabi et al. [61]	50	33	22	65	13	67	39	26	25
Pharmacological Management of Depression: Japanese Expert Consensus [62]	50	31	21	59	31	56	20	24	25
South Africa, Emsley [63]	50	48	19	67	13	19	26	12	33
USA, Connolly and Thase [64]	63	17	17	52	13	72	15	6	14

Country / Study	AGREE II domains' scores						AGREE-REX domains' scores		
	1. Scope and purpose	2. Stakeholder involvement	3. Rigour of development	4. Clarity of presentation	5. Applicability	6. Editorial independence	1. Clinical applicability	2. Values and preferences	3. Implementabilit
Korea, Wang et al. [65]	56	13	17	43	6	58	19	10	36
USA, Park and Zarate [66]	33	22	17	50	18	31	17	13	14
Canada, Voineskos et al. [67]	44	11	15	50	10	22	15	1	17
USA, Voytenko et al. [68]	54	39	15	65	8	42	17	8	22
Poland, Piotrowski et al. [69]	54	26	15	72	25	50	33	6	14
Australia, Bayes and Parker [70]	46	22	14	48	7	33	11	1	11
Australia, Malhi et al. [71]	44	20	13	63	17	39	17	7	25
France, Doumy et al. [72]	39	9	13	39	8	36	9	3	22
Canada, Mulsant et al. [73]	50	28	13	61	8	36	15	11	31
Depresja oporna na leczenie – zalecenia Konsultanta Krajowego w dziedzinie psychiatrii [74]	52	22	12	65	36	3	24	8	31
India, Avasthi and Grover [75]	70	24	12	80	36	0	22	7	31
Several countries, Möller et al. [76]	28	15	12	11	10	33	19	14	25
France, Charpeaud et al. [77]	33	13	10	46	10	36	13	0	19
USA, Busch and Sandberg [78]	46	11	10	65	15	17	19	6	25
USA, Mathys and Mitchell [79]	41	19	8	37	6	58	18	3	19
USA, Taylor [80]	41	7	8	57	8	33	22	7	33
Austria, Gartlehner et al. [81]	37	26	8	33	14	17	18	7	25
Spain, Pereira Sanchez and Santos [82]	54	24	6	61	8	33	15	7	22
India, Gautam et al. [83]	39	20	6	57	15	0	22	6	25
USA, Halaris [84]	41	17	6	31	13	11	18	5	30
Poland, Patejuk-Mazurek [85]	15	6	5	43	17	0	7	1	19

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