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

Franciele Cordeiro Gabriel, Airton Tetelbom Stein, Daniela Oliveira de Melo, Géssica Caroline Henrique Fontes-Mota, Itamires Benício dos Santos, Aliandra Fantinell de Oliveira, Renério Fráguas, Eliane Ribeiro

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 Library and 12 databases recognised as CPGs repositories. CPGs quality was assessed using the Appraisal of Guidelines for Research and Evaluation II (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 recognised 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 recognised 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, adherence to treatment, and increase dosage as first steps. All CPGs recommend psychotherapy, switching antidepressants, 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, adherence to treatment, increase dosage of antidepressants, and psychotherapy as first steps.

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 owing to its incapacitating nature. 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.5

The number of depressed persons has increased considerably.1 This situation overburdens the healthcare system and generates a greater need for resource optimisation.5 Thus, developing evidence-based interventions to achieve effective results is a pressing challenge in the mental health field.6 Moreover, owing to the COVID-19 pandemic, an increase in mental illnesses is expected, perhaps persisting for several years. There will be an even greater need to optimise resources for dealing with this significant challenge.7 A survey by the WHO9 showed that the COVID-19 pandemic had suspended essential mental health services in about 93% of countries worldwide while the population increasingly needs mental healthcare.

Clinical practice guidelines (CPGs) are fundamental to optimise these mental health resources, which will be in greater demand with the increased incidence of depression.9 These CPGs contain recommendations for optimising 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 first-line pharmacological treatment for 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 clinical recommendations by mental health professionals 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 CPGs for the treatment of depression in adults who have shown an inadequate response to first-line treatment.

MATERIALS AND METHODS
A broad 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 Appraisal of Guidelines for Research and Evaluation II (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 practice16 were compared with a method applied in a previous study published by the authors.13

Identification of CPGs (Search data source)
A comprehensive search was conducted on PubMed, Embase and the Cochrane Library for CPGs published from 1 January 2011 to 22 August 2020 (online supplemental appendix 1). We consulted twelve databases traditionally recognised as CPGs repositories.15 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, and 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 (GCHF-M), 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% in domain 3 of AGREE II—considered of high-quality; or were among 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 forms18 were used by two independent reviewers for data extraction. A third reviewer resolved the discrepancies. The following data were extracted: type of organisation that produced the CPG (government organisation or specialised society), country, method used to classify the evidence and the CPG development
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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 most commonly used in clinical practice, and being developed by an important CPGs developer institution. Domain 3 (rigour of development) was used to classify a CPG as ‘high-quality’ since this is the most important item regarding the reliability of the recommendations. Two independent researchers extracted all recommendations from the included CPGs. 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 synthesised 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 Library (n=105), and Embase (n=1155), and 44 additional records through the other 12 specific websites for CPGs. After removing 165 duplicates, 1993 documents remained. From those, we included 46 CPGs for quality assessment and selected eight of them for analysis of recommendation (figure 1). Online supplemental appendix 2 includes the reasons for including/excluding documents. Five CPGs that presented an AGREE II domain 3 score 280% were considered high-quality and selected. Two others (from The Canadian Network for Mood and Anxiety Treatments—CANMAT21 and from the American Psychiatric Association—APA-Psychiatry22) were also selected based on their widespread acceptance16 and an additional one (from the US Department of Veterans Affairs (VA), US Department of Defense (DoD)—VA/DoD CPG 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)—UK, score=84%;26 Depression, Adults in Primary Care from Institute for Clinical Systems Improvement (ICSI) Healthcare Guideline—US, score=81%;27 CPG for the Treatment of Depression across Three Age Cohorts from the American Psychological Association (APA-Psychology)—US, score=81%;28 VA/DoD CPG for the Management of Major Depressive Disorder from

Figure 1 Flowchart of clinical practice guidelines selection. CPGs, clinical practice guidelines.
Table 1  CPGs identified for quality assessment and AGREE-II scores

| CPG; author, year | AGREE II domain score (%) | Organisation | Location | Grading* | Development† |
|-------------------|---------------------------|--------------|----------|----------|--------------|
| Ministerio de Salud (Chile), 2012 | 83 76 89 94 57 17 | Governmental | Chile | GRADE‡ | New |
| Ministerio de Salud (Colombia), 2015 | 100 85 86 100 96 92 | Governmental | Colombia | GRADE | Adapted |
| NICE, 2018 | 89 83 84 81 71 75 | Governmental | England | GRADE | New |
| Triangle et al, 2016 | 96 78 81 91 72 97 | Consortium | US | GRADE | New |
| American Psychological Association–Depression Guideline Development Panel, 2019 | 91 67 81 80 57 83 | Specialty society | US | GRADE | New |
| VA/DoD, 2016 | 93 76 78 94 38 58 | Specialty society | US | GRADE | New |
| KPCMI, 2012 | 83 63 76 93 46 58 | Specialty society | US | GRADE | Adapted |
| Minsan Spain, 2014 | 94 93 70 91 57 53 | Governmental | Spain | Own method | New |
| RNAO, 2016 | 72 74 69 80 76 86 | Specialty society | Canada | Own method | New |
| Perez-Bryan et al, 2011 | 70 44 69 80 50 69 | Governmental | Spain | GRADE | New |
| Qaseem et al, 2016 | 80 39 69 70 32 67 | Specialty society | US | GRADE | New |
| Instituto Mexicano del Seguro Social, 2011 | 87 46 69 83 14 67 | Governmental | Mexico | Own method | Adapted |
| Instituto Mexicano del Seguro Social, 2015 | 81 43 69 80 32 31 | Governmental | Mexico | Several | Adapted |
| Instituto Mexicano del Seguro Social, 2016 | 94 56 63 81 42 64 | Governmental | Mexico | Several | New |
| Chua et al, 2012 | 78 72 60 89 50 28 | Governmental | Singapore | Own method | Adapted |
| Malhi et al, 2015 | 74 63 58 78 24 67 | Governmental | Australia | NA | New |
| Driot et al, 2017 | 69 30 56 72 11 83 | Independent authors | France | NA | New |
| Bauer et al, 2013 | 61 54 54 83 32 75 | Governmental | Several | Own method | New |
| Kennedy et al, 2016 | 63 48 54 89 26 53 | Specialty society | Canada | Own method | New |
| Dua et al, 2011 | 69 74 50 74 29 75 | Governmental | Several | GRADE | New |
| McIntyre et al, 2017 | 87 56 48 83 32 69 | Specialty society | US | Own method | New |
| Bauer et al, 2015 | 69 48 47 61 28 75 | Specialty society | Several | Own method | New |
| Malaysian Health Technology Assessment Section, 2019 | 81 50 47 70 54 78 | Governmental | Malaysia | SIGN adapted | New |
| Gelenberg et al, 2010 | 48 43 46 83 44 42 | Specialty society | US | Own method | New |
| Cleare et al, 2015 | 67 57 40 69 13 58 | Specialty society | England | Own method | New |
| Ruberto et al, 2020 | 43 11 35 39 1 72 | Independent | US | NA | New |
| BC Guidelines Canada, 2013 | 85 37 35 85 39 42 | Governmental | Canada | Own method | New |
| Giakoumatos et al, 2019 | 61 19 33 83 26 75 | Specialty society | US | NA | New |
| Bauer et al, 2017 | 56 41 23 76 21 50 | Specialty society | Several | Own method | New |
| Bennabi et al, 2019 | 50 33 22 65 13 67 | Specialty society | France | NA | New |
| Grobler, 2013 | 50 48 19 67 13 19 | Specialty society | South Africa | NA | New |
| Connolly et al, 2011 | 63 17 17 52 13 72 | Independent | US | NA | New |
| Wang et al, 2017 | 56 13 17 43 6 58 | Specialty society | Korea | NA | New |
| Park et al, 2019 | 33 22 17 50 18 31 | Independent | US | NA | New |
| Voineskos et al, 2020 | 44 11 15 50 10 22 | Independent authors | Canada | NA | New |

Continued
the US Department of VA, US DoD, score=78%23; Clinical guidelines for the management of adults with major depressive disorder from the CANMAT 2016—from Canada, score=54%21; Practice Guideline for the Treatment of Patients with Major Depressive Disorder from the APA, 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 presents a detailed description of the management strategies proposed by the most relevant CPGs concerning inadequate response to first-line treatment.

Terminology for responsiveness to the first line treatment and clear definition of terminology varied among CPGs. We found the terms remission, response, partial response, no response, inadequate response, refractory or resistant to treatment21 (table 2). Among the eight most relevant CPGs, four (50%) used the terms but did not present a clear definition of them22 23 25 26 (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%). The majority of CPGs emphasised the importance of adjusting antidepressant dose (7/8, 87.5%) in cases where patients do not respond to first-line treatment. However, only the NICE26 and CANMAT21 CPGs establish 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 four (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 guideline22 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 antidepressant while others did not make such distinction. The APA-Psychiatry28 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 25 26 27 28

Regarding combining and augmentation, only the MS Chile guideline24 established a sequency between them, recommending combining and augmentation strategies.21 23 24 26–28

**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

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**Table 1 Continued**

| CPG; author, year | AGREE II domain score (%) | Organisation | Location | Grading† | Development† |
|-------------------|---------------------------|-------------|----------|----------|--------------|
| Voineskos et al, 201656 | 54 39 15 65 8 42 | Independent | US | NA | New |
| Piotrowski et al, 201757 | 54 26 15 72 25 50 | Specialty society | Poland | NA | New |
| Bayes et al, 201958 | 46 22 14 48 7 33 | Independent authors | Australia | NA | New |
| Malhi et al, 201359 | 44 20 13 63 17 39 | Governmental | Australia | NA | New |
| Mulsant et al, 201460 | 50 28 13 61 8 36 | Governmental | Canada | NA | New |
| Avasthi et al, 201861 | 70 24 12 80 36 0 | Independent authors | India | NA | New |
| Möller et al, 201262 | 28 15 12 11 10 33 | Governmental | Several | NA | New |
| Busch et al, 201263 | 46 11 10 65 15 17 | Independent authors | US | NA | New |
| Taylor, 201464 | 41 7 8 57 8 33 | Independent authors | US | NA | New |
| Sánchez et al, 201965 | 54 24 6 61 8 33 | Independent authors | Spanish | NA | New |
| Gautam et al, 201766 | 39 20 6 57 15 0 | Independent authors | India | NA | New |

*Grading of evidence system.
†Method of clinical practice guideline development.
‡Modified version of GRADE.

AGREE II, Appraisal of Guidelines for Research & Evaluation II; APA-Psychology, American Psychological Association; BC, British Columbia; CPG, Clinical Practice Guideline; IMSS, Instituto Mexicano del Seguro Social; KPCMI, Kaiser Permanente Care Management Institute; MH, Ministry of Health; MS, Ministerio de Salud (Ministry of Health); NA, not available; NICE, National Institute for Health and Care Excellence; RNAO, Registered Nurses’ Association of Ontario; SIGN, Scottish Intercollegiate Guidelines Network; VA/DoD, US Department of Veterans Affairs (VA).
| CPG; author, year       | Terminology for responsiveness                                                                 | Recommended strategies                                                                                                                                 |
|------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ministerio de Salud (Chile), 2012<sup>24</sup> | 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 |
| Ministerio de Salud (Colombia), 2015<sup>25</sup> | 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<sup>26</sup> | 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<sup>27</sup> | 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. Optimise 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 specialised 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 hospitalisation |
| APA-Psychology, 2019<sup>28</sup> | 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-behavioural therapy, or psychodynamic therapy)  
4. Augment with another antidepressant medication (do not include augment with other medicines) |
| VA/DoD, 2016<sup>29</sup> | Partial response:<50% improvement in symptoms  
Response: improvement >50% PHQ scores  
Remission: PHQ score <4 for at least 1 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. |


### Table 2 Continued

| CPG; author, year | Terminology for responsiveness | Recommended strategies |
|-------------------|--------------------------------|------------------------|
| Kennedy et al, 2016 (CANMAT) | Partial response: 25%–49% reduction in symptom scores. No response: <25% reduction in symptom scores. Inadequate response: partial response and no response | 1. Optimise 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 (eg, 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 (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 4–8 weeks—switch to a different antidepressant, change to or augmentation with psychotherapy, augmentation therapy with other antidepressant or other medicine, or electroconvulsive therapy. |

AGREE II, Appraisal of Guidelines for Research and Evaluation II; APA-Psychiatry, American Psychiatric Association; APA-Psychology, American Psychological Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; CPG, Clinical Practice Guideline; ICSI, Institute for Clinical Systems Improvement; MS, Ministerio de Salud; NA, not available; NICE, National Institute for Health and Care Excellence; PHQ, Patient Health Questionnaire; SSRI, Serotonin Selective Reuptake Inhibitor; TCA, Tricyclic Antidepressants; VA/DoD, US Department of Veterans Affairs (VA).
## 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                  |
|                                                                    | MS Colombia, 2015                |
|                                                                    | Nice, 2015                       |
|                                                                    | Trangle et al, 2016 (ICSI)       |
|                                                                    | VA/DoD, 2016                     |
|                                                                    | APA-Psychology, 2019             |
|                                                                    | Kennedy et al, 2016 (CANMAT)     |
|                                                                    | Gelenberg et al, 2010 (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    | – 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                                             | ✔                                |

*Not listed in the recommendations section but mentioned in the clinical practice guideline.

APA-Psychiatry, American Psychiatric Association; APA-Psychology, American Psychological Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; CPG, Clinical Practice Guideline; ICSI, Institute for Clinical Systems Improvement; MS, Ministerio de Salud; NICE, National Institute for Health and Care Excellence; NPT, non-pharmacological treatment; VA/DoD, US Department of Veterans Affairs (VA).
Disorders V (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 different years, and the APA-Psychiatry, published in 2010, the oldest included, received the worst score on quality of rigour 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, standardised 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. 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. MacQueen et al., 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. Five CPGs recommend switching to another antidepressant before combining or augmentation strategies. 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, their recommendation is first switch to a more efficacious antidepressant, then to combination or augmentation and then switch to a second-line or third-line antidepressant. CPGs are not consensus 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. The CANMAT guideline, uses the term ‘adjunctive treatment’ to denominate combination for two antidepressants or augmentation with other medicine; the APA-Psychiatry use the denomination ‘augment’ to the use of two antidepressant. Also, the APA-Psychiatry guideline 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 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 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. On the other hand, other CPGs as the APA-Psychiatry guideline 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 frameworks as it is recommended.

Although most CPGs are congruent with the inclusion of antipsychotics, lithium and T3 as augmentation strategies to antidepressant treatment they usually do not establish the sequence among them.

**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 minimise 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 three extra CPGs among the most relevant in clinical practice, 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 is relevant to point out that discrepancies among CPGs have led health professionals to be hesitant in applying CPGs in clinical practice. Improvement in quality will help healthcare professionals in the implementation of CPGs. Acceptance by clinicians is the key for CPGs 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.
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/combination 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 different definitions in specific recommendations for non-responsive patients, mainly in their recommended sequence of strategies. Additionally, some do not present a standardised 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.

AUTHOR AFFILIATIONS
1 Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, São Paulo, Brasil
2 Departamento de Saúde Coletiva, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brasil
3 Curso de Pós-graduação em Avaliação de Tecnologia em Saúde, Hospital Conceição, Porto Alegre, Rio Grande do Sul, Brasil
4 Departamento de Ciências Farmacêuticas, Instituto de Ciências Ambientais, Químicas e Farmacêuticas, Universidade Federal de São Paulo, Diadema, São Paulo, Brasil
5 Departamento de Desenho Industrial, Universidade Federal de Santa Maria, Santa Maria, Rio Grande do Sul, Brasil
6 Laboratório de Neuro-imagem em Psiquiatria - LIM-21, Departamento e Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo; Divisão de Psiquiatria e Psicologia, Hospital Universitário, Universidade de São Paulo, São Paulo, São Paulo, Brasil

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Author affiliations
1 Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, São Paulo, Brasil
2 Departamento de Saúde Coletiva, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brasil
3 Curso de Pós-graduação em Avaliação de Tecnologia em Saúde, Hospital Conceição, Porto Alegre, Rio Grande do Sul, Brasil
4 Departamento de Ciências Farmacêuticas, Instituto de Ciências Ambientais, Químicas e Farmacêuticas, Universidade Federal de São Paulo, Diadema, São Paulo, Brasil
5 Departamento de Desenho Industrial, Universidade Federal de Santa Maria, Santa Maria, Rio Grande do Sul, Brasil
6 Laboratório de Neuro-imagem em Psiquiatria - LIM-21, Departamento e Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo; Divisão de Psiquiatria e Psicologia, Hospital Universitário, Universidade de São Paulo, São Paulo, São Paulo, Brasil

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ORCID iDs
Franciele Cordeiro Gabriel http://orcid.org/0000-0002-4375-3729
Arton Teletobim Stein http://orcid.org/0000-0002-7836-8699
Daniela Oliveira de Melo http://orcid.org/0000-0001-8613-7963
Géssica Carolina Henrique Fontes-Mota http://orcid.org/0000-0003-1986-9155
Itamires Benicio dos Santos http://orcid.org/0000-0002-8693-3121
Ailândra Fantinell de Oliveira http://orcid.org/0000-0001-7678-1614
Renério Fráguas http://orcid.org/0000-0002-3052-066X
Eliane Ribeiro http://orcid.org/0000-0003-0886-368X

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