Review of the guidelines of the Brazilian Medical Association for the treatment of depression (Full version)

Revisão das diretrizes da Associação Médica Brasileira para o tratamento da depressão (Versão integral)

Marcelo P. Fleck,[1,2] **Marcelo T. Berlim,**[3,4] **Beny Lafer,**[5,6] **Everton Botelho Sougey,**[7,8] **José Alberto Del Porto,**[9] **Marco Antônio Brasil,**[10,11] **Mário Francisco Juruena,**[12,13] **Luis Alberto Hetem**[14]

Abstract

Objective: *Depression is a frequent, recurrent and chronic condition with high levels of functional disability. The Brazilian Medical Association Guidelines project proposed guidelines for diagnosis and treatment of the most common medical disorders. The objective of this paper is to present a review of the Guidelines Published in 2003 incorporating new evidence and recommendations.* ***Method:*** *This review was based on guidelines developed in other countries and systematic reviews, randomized clinical trials and when absent, observational studies and recommendations from experts. The Brazilian Medical Association proposed this methodology for the whole project. The review was developed from new international guidelines published since 2003.* ***Results:*** *The following aspects are presented: prevalence, demographics, disability, diagnostics and sub-diagnosis, efficacy of pharmacological and psychotherapeutic treatment, costs and side-effects of different classes of available drugs in Brazil. Strategies for different phases of treatment are also discussed.* ***Conclusion:*** *The Guidelines are an important tool for clinical decisions and a reference for orientation based on the available evidence in the literature.*

Descriptors: *Depression; Review; Diagnosis; Treatment outcome; Sociology, medical*

Resumo

Objetivo: *A depressão é uma condição freqüente, em geral recorrente e de curso crônico, associada com níveis altos de incapacitação funcional. A Associação Médica Brasileira, por meio do projeto "Diretrizes", buscou desenvolver guias para diagnóstico e tratamento das doenças mais comuns. O objetivo deste trabalho é o de atualizar as Diretrizes desenvolvidas em 2003, incorporando novas evidências e recomendações.* ***Método:*** *A metodologia utilizada foi a proposta pela Associação Médica Brasileira para o projeto Diretrizes. Assim, o trabalho foi baseado em diretrizes desenvolvidas em outros países aliadas a artigos de revisão sistemáticos, ensaios clínicos randomizados e, na ausência destes, estudos observacionais e recomendações de grupo de* experts*. A atualização foi realizada a partir de novas diretrizes internacionais publicadas a partir de 2003.* ***Resultados****: São apresentados dados referentes a prevalência, demografia, incapacitação, diagnóstico e subdiagnóstico de depressão. Em relação ao tratamento, são mostrados dados sobre a eficácia do tratamento medicamentoso e psicoterápico das depressões, além do perfil de custos e de efeitos colaterais das diferentes classes de medicamentos disponíveis no Brasil, além do planejamento das diferentes fases do tratamento.* ***Conclusão:*** *As diretrizes têm como objetivo servir de orientação para a tomada de decisões clínicas baseada nas evidências científicas da literatura disponível.*

Descritores: *Depressão; Revisão; Diagnóstico; Resultado de tratamento; Sociologia médica*

[1] Department of Psychiatry and Legal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre (RS), Brazil
[2] Mood Disorders Program (PROTHUM), Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre (RS), Brazil
[3] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[4] Douglas Mental Health University Institute, Montreal, Quebec, Canada
[5] Department of Psychiatry, Medical School, Universidade de São Paulo (USP), São Paulo (SP), Brazil
[6] Bipolar Disorder Program (PROMAN), Institute of Psychiatry, Clinical Hospital, Medical School, Universidade de São Paulo (HC-FMUSP), São Paulo (SP), Brazil
[7] Department of Neuropsychiatry, Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil
[8] Assistance, Teaching and Research Nucleus on Affective Disorders, Clinical Hospital, Universidade Federal de Pernambuco (UFPE), Recife (PE), Brazil
[9] Paulista Medical School (EPM), Universidade Federal de São Paulo (Unifesp), São Paulo (SP), Brazil
[10] Medical School, Universidade Federal do Rio de Janeiro (UFRJ) Rio de Janeiro (RJ), Brazil
[11] Former President of the Brazilian Psychiatry Association
[12] Department of Neurosciences and Behavioral Sciences, Psychiatric Division, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil
[13] Section of Neurobiology of Mood Disorders, Institute of Psychiatry, King's College London, London, UK
[14] Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil

Correspondence
Marcelo Pio de Almeida Fleck
Departamento de Psiquiatria e Medicina Legal
Universidade Federal do Rio Grande do Sul
Rua Ramiro Barcelos, 2350 - 4º andar
90430-090 Porto Alegre, RS, Brasil
Telephone: (+55 51) 3316-8413 Fax: (+55 51) 3330-8965
Email: mfleck.voy@terra.com.br

Introduction

Depression is a relatively common condition,[1] with a chronic[2] and recurrent course.[3-5] It is frequently associated with functional impairment[6] and the compromising of the physical health.[7-9] Depressed patients show limitation in their activity and well-being,[10,11] besides a higher utilization of health services.[12]

However, depression is still under-diagnosed and under-treated. Between 30 and 60% of depression cases are not detected by the general clinician in primary care units.[13,14] Many times, depressed patients also do not receive sufficiently adequate and specific treatment.[15] The morbimortality associated with depression can be, in a good proportion, prevented (in nearly 70%) with the correct treatment.[16]

In the year 2001, the Brazilian Medical Association (AMB) developed the Guidelines Project, aimed at establishing guidelines for the identification and treatment of a series of common medical conditions, among them depression. In 2003, the *Revista Brasileira de Psiquiatria* (RBP) published a more detailed version of these guidelines.[17] Recently, following an initiative of the AMB, these guidelines were reviewed and the RBP asked the authors to publish a new more detailed version of this review on depression.

Therefore, the main objective of this article was to review and update the Guidelines for Depression published in 2003, emphasizing the diagnosis and treatment of unipolar depression. The original objectives of the guidelines are the same, namely: 1) to provide subsidies to enhance the capability of diagnosing new cases of depression; 2) to provide a rational approach for the treatment of depression, defining which cases should be treated, how to treat them, and when to refer them to the psychiatrist/specialist;3) to raise the professionals' conscience about the importance of their role in reducing the impact of morbidity-mortality and improving the depressed patients' quality of life.

Method

The original guidelines of 2003 were based on four documents developed by renowned institutions or groups: British Association for Psychopharmacology,[18] American Psychiatric Association,[19] Department of Health and Human Resources of the United States *(*Depression Guideline Panel*)*[20,21] and the Committee for the Prevention and Treatment of Depression of the World Psychiatric Association.[22] The criterion to select these documents was having used mainly systematic review articles, randomized clinical trials and in their absence, observational studies and recommendation of an expert group. Most data used in these studies were of depressed patients who sought psychiatric services, due to the small (although rising) number of studies based on patients of primary care service.

For this review we made a search in Pubmed using the keyword "*unipolar depression*". The search was limited by the type of article (practice guidelines), language (English) and year (from 2002 onward). With this search we found 23 publications. Their abstracts were examined, being selected five which met the criteria of the guidelines for the diagnosis and treatment of unipolar depression in adults.[23-27]

The main complimentary and innovative elements of these documents were added to the Guideline published in 2003.

Part 1 - Depression: prevalence and diagnosis

Depression is a frequent problem

Prevalence studies in Western countries show that depression is a frequent disorder. The annual prevalence in the general population varies from 3 to 11%.[28-30] One meta-analysis of 23 studies of prevalence and incidence of depression, using the sample pool, found a prevalence of 4.1% in one year and 6.7% in lifetime.[1] These data contrast with the main American study on the subject, which found respectively 6.6% (one year) and 16.2% (in lifetime).[3]

Studies developed with clinical samples (of patients) show a higher prevalence. In patients of primary care health services, Ustun e Sartorius,[31] in an international study accomplished in 14 countries, showed a prevalence median above 10%. In specific populations, such as of patients with recent stroke, it reaches 33%,[32] achieving 47% in cancer patients.[33] In hospitalized patients due to any physical disease, the prevalence of depression ranges from 22% to 33%.[22]

Depression is more frequent among women

The prevalence of depression is two to three times more frequent in women than in men, even considering studies accomplished in different countries, communities or patients who seek psychiatric services.[34]

Depression is a chronic and recurrent disorder

Nearly 80% of the individuals who received a treatment for a depressive episode will have a second episode in their lifetime, being the median of four in lifetime.[18] The mean duration of an episode ranges from 16 to 20 weeks and 12% of the patients have a chronic course without symptom remission.[35,36]

Depression is an incapacitating disorder

Using a global scale to compare several diseases, the estimations are that depression was the fourth specific cause of incapacitation in the 1990's. The forecast for the year 2020 is that it will be the second cause in developed countries and the first in developing countries.[37] When compared to the main chronic medical conditions, depression is only equivalent, in terms of incapacitation, to severe cardiac ischemic diseases,[6] causing more impairment in the health status than angina, arthritis, asthma and diabetes.[38]

Depression is scarcely diagnosed by non-psychiatric physicians

In primary care services and other general medical services, 30 to 50% of depression cases are not diagnosed.[13,14,39]

The reasons for this under-diagnosis stem from factors related to patients and physicians. Patients may have prejudice regarding the diagnosis of depression and disbelief in relation to the treatment. The factors related to physicians include lack of training, lack of time, disbelief regarding the effectiveness of the treatment, recognition only of the physical symptoms of depression and identification of the symptoms of depression as an "understandable" reaction".[40,41]

The training of non psychiatric physicians to diagnose depression, as well as the use of screening instruments for depression have not shown neither a substantial nor an enduring impact on the appropriate management of depression cases.[42,43] The detection of depression by the non psychiatric physician does not seem to be associated with the adequate indication of treatment.[44]

There are simple questions which help to improve the detection of depression by the physician

The modern classificatory systems in psychiatry operationalized the diagnosis of depression, facilitating its recognition and the scientific communication between professionals (Table 1).

Table 1 - Diagnostic criterion of depressive episode according to the ICD-10*[45]

Main symptoms
1. Depressed mood
2. Loss of interest
3. Fatigability
Accessory symptoms
1. Reduced concentration and attention
2. Reduced self-esteem and self-confidence
3. Ideas of guilt and unworthiness
4. Bleak and pessimistic views of the future
5. Disturbed sleep
6. Diminished appetite

** Mild episode: 2 fundamental + 2 accessory symptoms*
Moderate episode: 2 fundamental + 3 to 4 accessory symptoms
Severed episode: 3 fundamental + > 4 accessory symptoms

In Table 2, we present some questions that can improve the detection of depression cases by non psychiatric physicians.

Besides the diagnosis of the depressive episode, there are other presentations of depression with less intense symptoms, although with a similar incapacitating degree, which are very frequent in primary care services

Dysthymia is a chronic depressive disorder with lower intensity of symptoms, which is present for at least two years with occasional and short periods of well-being. Besides the depressed mood, there should be present up to three of the following symptoms: low energy, insomnia, low self-esteem, poor concentration, crying, decreased sexual drive as well as of other pleasant activities, feeling of hopelessness and distress, difficulty of dealing with daily responsibilities, pessimism in relation to the future, social withdrawal, and slowed speech.[45] Evidence of other naturalistic studies shows that the impairment of the social and occupational functioning in dysthymia is higher than that of depressive episodes,[6,48-51] suggesting that the extension of the social and occupational impairment be more related to the duration of symptoms than to their intensity.

Mixed anxiety and depression disorder includes patients with anxiety and depression symptoms and none of the set of symptoms considered separately is sufficiently intense to justify a diagnosis. In this disorder, some autonomic symptoms (trembling, palpitation, dry mouth, stomach pain) may be present, even though intermitently.[45] Its prevalence is 4.1% in primary health services treating this disorder.[52,53]

Recently, a particular attention has been given to mildly depressed patients who do no meet the diagnostic criteria (subsyndromic depression), but who have high risk of presenting with future depressive episodes.[22]

Before starting an antidepressant treatment it is important to exclude a diagnosis of bipolar disorder

Nearly 10 to 20% of unipolar depressed patients have their diagnosis changed to bipolar mood disorder along time.[54,55] It is highly clinically relevant to know that antidepressants may trigger mania in patients with apparent unipolar disorder.[56]

Part 2: Treatment

1. General considerations

Antidepressants are effective in the acute treatment of moderate and severe depressions, however, they do not differ from placebo in mild depressions

There is striking evidence in the literature that antidepressants are efficient in the treatment of moderate to severe acute depression, either improving the symptoms (response) or eliminating them (full remission).[18]

Table 2 – Questions to screen depression[18]

Two-question test[46]
1. In the last mont have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by little interest or pleasure in doing things?
Yes for both questions: Sensitivity = 96%. Specificity = 57%
Goldberg scale for the detection of depresion[47]
Have you been having low energy?
1. Have you had loss of interest?
2. Have you had loss of self-confidence?
3. Have you felt hopeless?
(If yes for anyone, continue...)
4. Have you had difficulty to concentrate?
5. Have you lost weight (due to low appetite)?
6. Have you been waking up early?
7. Have you doing things more slowly?
8. Do you tend to feel worse in the morning?
Yes for three or more: Sensitivity = 85%. Specificity = 90%

The response rate in intention-to-treat samples range from 50 to 65%, against 25 to 30% shown by placebo in randomized clinical studies.[21,57,58] A systematic review of antidepressant treatment in depressive disorder associated with physical disease showed similar response rates.[57,59] Other review of meta-analysis studies of depressed patients treated in primary care services showed response rates between 50 and 60%, which are similar to those obtained in samples of psychiatric patients.[57]

Antidepressants did not show advantages in relation to placebo in mild depressions, as a good response is observed in both.[60-62]

In patients with psychotic depression, the association of antidepressants with antipsychotics is more effective antidepressants alone

There is consistent literature showing that antidepressants or antipsychotics used alone have worse result than when combinedly used.[63,64] Both typical and atypical antipsychotics are effective, and there are no controlled data that compare "new" *versus* "old" antipsychotics.[25]

The full remission of symptoms should be the goal of any antidepressant treatment

There is consistent evidence in the literature that the permanence of residual depression symptoms are associated with worse quality of life, worse functionality, higher suicide risk, higher relapse rate and increased consumption of health services.[65,66]

Antidepressants are effective in the acute treatment of dystymia

One meta-analysis of 15 randomized clinical trials for the treatment of dystymia showed that 55% of the patients respond to antidepressants, compared to 30% with placebo.[67]

Specific psychological treatments for depressive episode are effective with higher evidence for mild to moderate depressions

Recent pieces of evidence established by review studies and meta-analysis have shown efficacy in the acute treatment of depressions for the following forms of psychological treatments: cognitive-behavioral psychotherapy,[68] behavioral psychotherapy,[69] interpersonal psychotherapy[70] and problem solving psychotherapy.[71] Other psychotherapies have also shown efficacy, although supported by a lower number of studies: brief psychodynamic psychotherapy,[72] marital therapy[73] and counselling.[74]

Evidence suggests 1) a similar efficacy for antidepressants, cognitive-behavioral behavioral and interpersonal psychotherapy or combined treatments in mild to moderate depressions; 2) a higher efficacy of combined treatments (antidepressants + psychotherapy) in moderate to severe depressions; and 3) an absence of evidence for very severe depressions.[24]

Different antidepressants have similar efficacy for the majority of depressed patients, varying in relation to the profile of side effects and the potential interaction with other medications

Systematic review and meta-analyses studies suggest that commonly available antidepressants have a comparable efficacy for the majority of patients seen in primary care or in outpatient services.[75-77]

The meta-analyses about side-effects in the acute use of antidepressants have been concentrated in the comparison between selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. The use of SSRIs is associated with a lower rate of treatment dropout as compared to tricyclic antidepressants, but the absolute difference is of only 3 to 5%.[18,78] However, this difference, may increase with the duration of treatment[18] and may be higher in the daily clinical practice.[79]

SSRIs antidepressants have more chance than tricyclic antidepressants to be prescribed in doses recommended for the recommended time.

There is consistent evidence that tricyclic antidepressants are prescribed in lower doses and for a shorter time than what is recommended.[80-84] Nevertheless, there is no direct evidence that patients who received SSRIs have a better result than those who received tricyclic antidepressants.[85]

New antidepressants are more expensive than older drugs, but it remains controversial if the general cost of treatment would be higher. There are no Brazilian data about costs.

The price of medications is one of the aspects of the treatment cost. Factors such as the number of consultations, examinations requested, work absences, relapses and hospitalization days are some of the other data to be taken into consideration. Some studies have shown that the general costs of treatment with SSRIs and tricyclic antidepressants are close.[86] However, most of pharmaeconomic studies have problems when it comes to outlying and/or conflict of interest, and their external validity is limited, as they refer to costs or routines which are specific to some centers or coutries.[18] There are no Brazilian data in relation to this subject.

The prescription of antidepressants is associated with the decrease of the risk of suicide.

Epidemiological studies in the last decades have revealed a decrease in the frequency of suicide with the prescription of antidepressants. Some data suggest that the treatment with SSRIs could increase the risk of suicide in some patients.[87] Such risk would be increased in the beginning of the treatment.[88] Comparatively, the risk of suicide is higher before starting the antidepressant treatment (prior month), being much lower in the first week of treatment, decreasing even more in the following weeks.[89]

2. Practical considerations

Weekly consultations in the beginning of the treatment are associated with higher adherence and better results in the short-term

Naturalistic studies that compared the usual routines of the services with weekly interviews in the first four to six weeks showed a better outcome and higher adherence of patients who followed the weekly regime.[57,90]

The need of monitoring the response, side-effects, treatment adherence and risk of suicide also reinforce the weekly frequency as the advisable one in the initial phase of the treatment.[18]

The response to acute treatment with antidepressants is observed within two to four weeks after the beginning of use; however, the beginning of response uses to occur in the fist week.

The clinically significant response to antidepressants is not immediate and uses to occur between the second and the fourth week of utilization.[18] However, the beginning of action seems to occur already in the first week. One meta-analysis of 46 studies showed that 35% of the improvement measured in assessment scales occur in the first week.[91] Improvement within the first two weeks of treatment is associated with higher chances of responding to treatment.[92,93] Absence of response within four weeks decreases the chance of subsequent response with the same treatment, although some patients could respond within six weeks.[94,95]

When a patient does not respond to the treatment the recommendation is to revise the factors related to non response:

1) correct diagnosis, assessing the possibility of a concurrent medical or psychiatric disease;[18]

2) adherence to treatment. The adherence to antidepressant treatment is relatively low, varying from 40 to 90% in different studies, being the mean equal to 65%;[96]

3) long duration of the disease;[97-100]

4) chronic social difficulties and persistent life events;[14,101,102]

5) severe episode or with psychotic symptoms;[5,103-108]

6) dystymia and severe personality disorder.[109-114]

The strategies used when a patient does not respond to the treatment with antidepressant medication consists of 1) increase of dose; 2) potentiation with lithium or triiodotironine (T3); 3) association of antidepressants; 4) change of antidepressant; 5) electroconvulsive therapy (ECT); and 6) association with psychotherapy

There is limited evidence about which strategy would be the best alternative in cases of non response to a treatment initially proposed.[115] One randomized study showed that the increase of fluoxetine up to 60mg in patients who had not responded to 20mg for eight weeks was more effective than potentiation with lithium or desipramine.[116]

Increase of the dose, when there is no response, seems to be a logical step, considering that there is a great individual variety in the plasma concentration of antidepressants and that there is uncertainty about which would an appropriate dose for a certain individual.[18]

There are no randomized studies comparing the continuation of an original treatment to the change for a different antidepressant. Controlled studies have methodological problems such as particular types of patients and small samples.[18] Open studies show that nearly 20 to 60% of patients respond to the change of antidepressants[21] or to the change between SSRIs.[117]

One meta-analysis of four randomized clinical trials demonstrated that the potentiation of antidepressants with lithium carbonate in treatment-resistant patients showed that nearly 40% responded as compared to 10% with placebo.[118]

One meta-analysis also with four randomized clinical trials assessing the effect of the potentiation with triiodotironine showed a moderate size effect (0,6) regarding the improvement in the depressive symptomatology when compared to placebo, but the difference was non significant in relation to the rate of response (8%).[119]

As for ECT, open studies show response rates of 50% in treatment-resistant depressed patients.[120]

There is some evidence that the association of antidepressant medication with cognitive-behavioral psychotherapy (CBT) or with interpersonal psychotherapy may improve the outcome of treatment-resistant patients who seek psychiatric services.[121,122] After an unsatisfactory response to antidepressants (SSRIs), patients assigned to receive different antidepressant strategies had outcomes similar to those who received CBT, being CBT better tolerated than the change by an antidepressant medication.[123] The potentiation of the antidepressant effect with CBT has started its effect later than antidepressants.[123]

The chance that a following antidepressant treatment be successful decreases at each failed attempt

The number of previous attempts with antidepressant medication is a predictive factor for the treatment's failure. Next step studies are, generally, problematic, for having small "n", being non replicated and having very heterogeneous populations, what make difficult generalizations.[24] One recent exception is the STAR*D project (Sequenced Treatment Alternatives for the Relief of Depression),

which involved nearly 4,000 patients followed-up along four stages in order to assess the performance of consecutive attempts with diverse antidepressant schemes.[124] One of the main findings of the STAR*D project was precisely that the response to treatment decreased from 49% to 19% and the remission decreased from 37% to 13% along the four study's stages.[125] Other recent studies corroborate the importance of absence of response to an antidepressant as a good predictive factor of unsatisfactory response to subsequent treatments.[36]

ECT is an acute treatment for depressions, being more efficient than antidepressant medications

Most studies with ECT involve severe and treatment-resistant patients. Meta-analyses show that ECT has a superior efficacy when compared to antidepressant medications.[126-128] There is evidence that, when ECT is used as a 4th stage in a sequential study of antidepressant treatments, 82% obtained a clinically significant response.[129]

Transcranial magnetic stimulation and vagal nerve stimulation (VNS) are new options for the treatment of depression; however, the evidence that supports their use is still preliminary

Transcranial magnetic stimulation consists of the stimulation of the cerebral cortex, by means of a magnetic field. Meta-analyses found significant clinical effects.[130,131] Nevertheless, the studies involved small samples, with a heterogeneous methodology, mostly studies exclusively on the acute phase, and few studies involve middle- and long-term follow-up.

VNS as an antidepressant treatment is based on its anatomical peculiarities, as it is projected to brain areas which are relevant for the generation and control of emotions.[132] VNS has not shown to be more efficient than a control group with simulated treatment,[133] although other studies with different doses have shown efficacy.[134] Despite being approved by the Food and Drugs Administration (FDA) as an adjunct treatment for resistant depression, up to the moment it is questionable if VNS exerts a higher effect than placebo or other treatments and more controlled studies are urgently needed.[135]

The planning of an antidepressant treatment involves the acute, the continuation and maintenance phases, each with specific objectives

The predominant model in the literature for the planning of antidepressant treatment involves the acute, continuation and maintenance phases.[136]

1) **Acute phase.** The acute phase includes two to three first months and has the objective of decreasing the depressive symptoms (response) or ideally the full attenuation with the return to the pre-morbid functioning level (remission).

2) **Continuation phase.** It corresponds to the four to six months which follow the acute treatment and aims to sustain the improvement obtained, preventing **relapses** within the same depressive episode. At the end of the continuation phase, patients who maintain the initial improvement are considered as **recovered** from the index episode.

3) **Maintenance phase**. The objective of the maintenance phase is to prevent the occurrence of new episodes (recurrence). The maintenance phase, therefore, is recommended for those patients who have probability of recurrence.

One third of the patients with depressive episode with initial remission relapse in the first year

The relapse rates decrease along time. They are estimated at 20 to 24% in the first two months, 28 to 44% at four months, 27 to 50% at six months and 37 to 54% at 12 months[137]. Similar results were described for depressed patients in general medicine outpatient settings with relapse of 37% within one year.[138]

Continuation antidepressant treatment for six months reduces the relapse risk in 50%

One meta-analysis of studies with patients in depressive episode treated with antidepressant for two to six months, besides remission, shows a relative risk of 0.5 when compared to placebo.[139]

The benefit of a treatment for more than six months after remission was demonstrated only for groups with history of recurrent depressive episodes.[18]

There are factors which seem to be associated with a higher risk of relapses/recurrences

The following factors seem to be associated with a higher risk of relapse/recurrence: 1) number of previous episodes;[140] 2) residual symptoms;[141] 3) severity of depressive symptoms;[142] 4) longer duration of the episode;[143,144] 5) psychosis;[145] 6) level of treatment resistance;[125] 7) female gender;[144,146] 8) social stress/small social adjustment;[141,147] and 9)life events.[148]

The effective dose of continuation treatment is the same of acute treatment

There are no controlled studies that define which is the best dose for a continuation treatment. Naturalistic studies show a benefit in continuing with the same dose of that of acute treatment when compared to reducing the dose.[149]

Maintenance treatment reduces the recurrence rate in patients with three or more episodes in the last five years

Controlled studies with patients with recurrent depressive episodes (typically three in the last five years) showed that the maintenance of an antidepressant medication prevents the recurrence in the following one to five years.[78] The follow-up of patients with prior recurrent episodes demonstrated that only 20% of the patients who had received antidepressants showed recurrence as compared to 80% of those who received placebo.[150]

One five-year naturalistic study showed a benefit of the sustained use of antidepressant beyond 28 weeks for patients who had had five or more prior episodes, but not for patients with less episodes.[149]

The effective dose for maintenance treatment is the same of acute treatment

Two controlled studies showed a higher recurrence rate in patients whose maintenance treatment was accomplished with half of the dose of acute treatment within the following two to three years,[150,151] suggesting that the effective dose in the acute phase should be maintained in the long-term as to prevent recurrences.

Lithium seems to be an alternative to the antidepressants in maintenance treatment of depressive episodes, with reduction in the risk of suicide

Two meta-analyses showed the superiority of lithium when compared to placebo in the maintenance treatment of depressive episodes,[152,153] and in one of them this difference was not statistically significant.[153] There was no difference on antidepressant medications in the prevention of relapses and recurrences in patients with unipolar depression in the period of five months to three years.[152,154]

One meta-analysis showed that lithium had a reduction of 85% in the suicide rate as compared to a group of patients who used antidepressants.[155]

The abrupt suspension of antidepressant medications is associated with the appearance of discontinuation symptoms

Controlled studies with SSRIs and venlafaxine and open studies and case reports with tricyclic antidepressants and MAO inhibitors show that the abrupt suspension of the antidepressant treatment can lead to discontinuation symptoms which occur from the first days up to three weeks.[156-159] Antidepressants have low potential for abuse[160] and there is no evidence that discontinuation reactions are part of a syndrome of antidepressant addiction.[161]

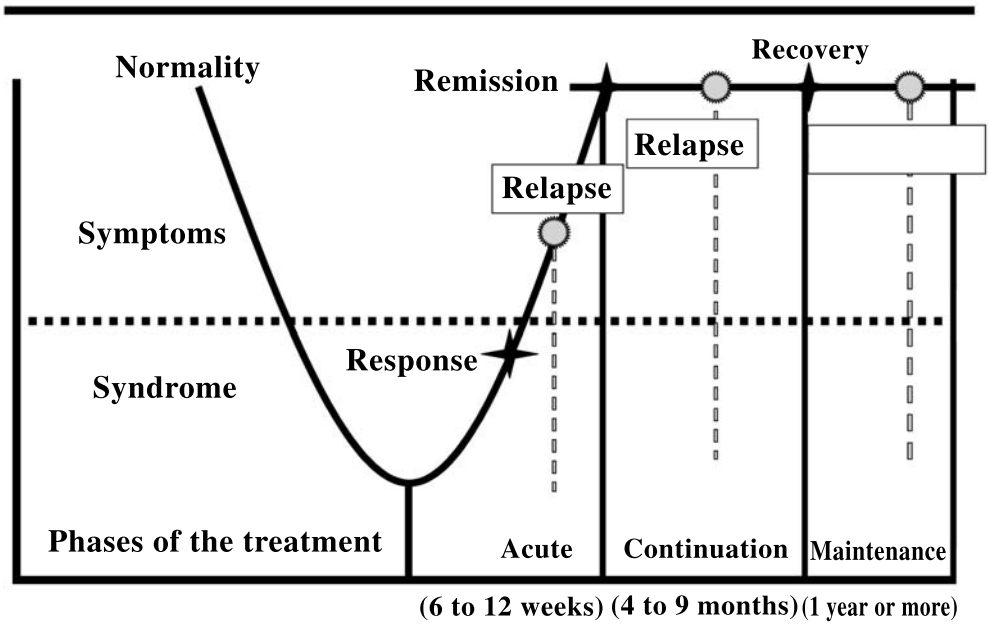

Figure 1 – Phases of the treatment of the depressive episode
(Based on Kupfer 1991)

Table 3 – Profile of side effects of antidepressant medications available in Brazil[24,25]

	Anticholinergic *	Sedation	Insomnia	Postural Hypotension	Nausea	Sexual dysfunction	Weight gain	Specific
Tryciclic								
Amytriptiline	++	++	-	++	-	+	++	
Chlomipramine	++	++	+	++	+	++	+	
Imipramine	++	+	+	++	-	+	+	
Nortryptiline	+	+	+	+	-	+	-	
SSRI								
Citalopram Escitalopram Sertraline	-	-	+	-	++	++	-	
Fluoxetine Fluvoxamine Paroxetine	-	-	+	-	++	++	-	
ISRNaS								
Venlafaxine	-	-	+	-	++	++	-	Hypertension
Desvenlafaxine	-	-	-	-	-	+	-	Hypertension
Duloxetine	-	-	+	-	++	++	-	-
Other RI								
Maproptiline	++	++	-	-	-	+	++	Seizures
Reboxetine	+	-	-	-	-	+	-	
Receptor antagonists								
Trazodone	-	++	-	++	-	-	+	Priapism
Mianserine	+	++	-	-	-	-	-	Blood dyscrasia
Mirtazapine	-	++	-	-	-	-	++	
MAOI					Ores			
Tranilcipromine	+	+	++	++	+	++	++	Hypertensive crisis
Moclobemide	-	-	+	-	+	-	-	
Dopamine agonists								
Bupropione	-	-	++	-	+	-	-	
ERS								
Tianeptine	+	+	-	-	+	-	-	
Others								
Agomelatine	-	-	-	-	-	-	-	-

++, relatively common or strong; + can occur or moderately strong; -, absent or rare/weak; ?, unknown/insufficient information
** Anticholinergic symptoms include dry mouth, sweating, blurred sight, constipation and urinary retention.*
SSRI = selective inhibitor of serotonin reuptake; RI = reuptake inhibitors; SRS = serotonin reuptake stimulator

APPENDIX
RECOMMENDATIONS[18]

I- REFERRAL TO/COUNSELING WITH PSYCHIATRIST BT THE NON SPECIALIST PHYSICIAN

The referral to the psychiatrist is indicated in the following situations:

1) risk of suicide;
2) psychotic symptoms;
3) history of bipolar affective disorder.

The referral to, or counseling with, a psychiatrist is appropriate in the following situations:

1) the physician feels incapable of dealing with the case;
2) two or more attempts of antidepressant treatment which failed or had partial response.

II- INDICATIONS OF ANTIDEPRESSANT TREATMENT

Moderate to severe depressive episodes and dystymia

The antidepressants medications are the first line of treatment independently from the presence of environmental factors.

Mild depressive episodes (first episode)

1) Antidepressants are not indicated;
2) education, support and simple solution of problems are recommended;
3) monitoring for the persistence or for the development of moderate to severe depressive episodes.

Mild to persistent depressive episodes

Therapeutic test with antidepressant medication.

Mild depressive episode in patient with previous history of moderate to severe depressive episode

Consider treatment with antidepressant.

Mild to moderate depressive episodes

Specific psychotherapies for depression (cognitive and interpersonal) are effective alternatives to the medications, depending on the availability of professionals and the patient's preference.

III- CHOICE OF THE ANTIDEPRESSANT MEDICATION

1) Individualize the treatment considering the patient's specific aspects;
2) in the absence of special factors, choose antidepressants that are well tolerated , safe when excessively taken and more likely to be taken in the prescribed doses. There is strong evidence regarding these criteria for SSRIs. However, mirtazapine, reboxetine and venlafaxine are also safe and well tolerated;
3) for severe depressive episodes in hospitalized patients, consider the use of tricyclic antidepressants or venlafaxine preferentially;
4) take into account also the following factors: a) prior response to a particular medication; b) tolerability and adverse effects in relation to a prior medication; c) side-effects profile (for example, weight gain, sedation, alterations in the sexuality); d) low lethality in case of present or past suicide risk ; e) concomitant physical disease that may hamper the use of an specific antidepressant; f) use of concomitant medications that might interact with the antidepressant medication; g) concomitant psychiatric disease that might respond to a specific antidepressant (for instance, obsessive-compulsive disorder and SSRI); h) the patient's preference; i) cost.

IV- THE MANAGEMENT OF AN ACUTE SITUATION

1) Reconsultations at each one or two weeks at the beginning of the treatment. Telephonic contacts by non medical trained health professionals can replace adequately some medical consultations;
2) at each revision, assess the response, adherence to treatment, collateral effects and risk of suicide;
3) educate the patient regarding the nature of the depressive disorder, of the side effects, of the benefits of the medication;
4) limit the dose of antidepressant provided considering the risk of suicide;
5) when prescribing a tricyclic or other antidepressant that need the progressive increase of the dose, increase the dose at each three to seven days as to allow the adjustment of side effects.

V- MANAGEMENT OF THE ABSENCE OF RESPONSE TO THE TREATMENT INITIALLY PROPOSED

1) Treat the depressive episode for at least four weeks before considering changing the strategy.
2) If there is absence of response within four weeks: a) check the dose and the adherence to the treatment; b) revise the diagnosis, including the possibility of the presence of psychiatric comorbidity or physical disease, that should thus receive treatment; c) consider the presence of social factors that should be dealt with if present.
3) If there is partial response within four weeks: a) continue the treatment for two weeks more.
4) If there is absence of response within four weeks (after verification of item 2) or partial response after six weeks:
a) increase the dose;
b) replace the dose by another class of a replace the dose with another class of antidepressants;
c) consider changing for MAOI in patients with atypical symptoms (weight gain, hypersomnia, hyper-sensitivity to criticism, reactive mood to external events).
5) Absence of response to a second antidepressant:
a) add a potentiating agent;
b) add psychotherapy;
c) electroconvulsive therapy.

NOTE: The use of potentiating agents, the prescription of MAOI and electroconvulsive therapy should be accomplished with psychiatric assistance or by a psychiatric service.

VI- CONTINUATION TREATMENT

1) Continue the antidepressant treatment for at least six months after the remission of the symptoms of the depressive episode;
2) in patients who persist with residual symptoms, maintain the treatment for a more prolonged time period;
3) maintain the same dose utilized in the acute phase;
4) in case of a relapse in the continuation phase, use the same principles of non response to treatment.

VII- MAINTENANCE TREATMENT

1) The maintenance treatment is indicated in the following situations: a) three or more depressive episodes in the last five years;
b) more than five episodes in lifetime; c) persistent risk of relapse.
2) maintain the same dose utilized in the acute phase;
3) The maintenance treatment should be accomplished for at least five years and, probably, indefinitely;
4) the recurrence of a depressive episode should be treated using the same principles of non response to treatment.

VIII- PRECAUTIONS TO BE ADOPTED WHEN DISCONTINUING AN ANTIDEPRESSIVE

1) In order to discontinue an antidepressant, gradually decrease the dose during, ate least, four weeks;
2) for patients in maintenance treatment, gradually decrease the dose along six months;
3) in case of a discontinuation reaction, explain and calm down the patient. In case of a more intense discontinuation reaction, the antidepressant should be reintroduced and discontinued more slowly.

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Marcelo P. Fleck	UFRGS HCPA	CNPq*** FIPE/HCPA*** Sixth Framework Programm: Comunidade Européia*	Bolsa de Produtividade CNPq*	-	-	Consultor temporário da Organização Mundial da Saúde	-
Marcelo T. Berlim	McGill	-	-	-	-	RBP	-
Beny Lafer	USP**	FAPESP*** CNPq***	APA/AstraZeneca Young Minds in Psychiatry International Awards***	Astra-Zeneca*	-	-	-
Everton Botelho Sougey	UFPE	-	-	-	-	-	-
José Alberto Del Porto	UNIFESP	FAPESP	-	AstraZeneca, Lilly, Abbott, Servier Solvay Wyeth	-	-	-
Marco Antônio Brasil	HUCFF/UFRJ	-	-	-	-	ABP	-
Mário Francisco Juruena	FMRP-USP	FAPESP***	National Institute for Health Research	Lilly*	-	UNESCO	-
Luis Alberto Hetem	FMRP-USP	-	-	-	-	-	-

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFRGS = Universidade Federal do Rio Grande do Sul; HCPA = Hospital de Cínicas de Porto Alegre; USP = Universidade de São Paulo; UNIFESP = Universidade Federal de São Paulo; UFPE = Universidade Federal de Pernambuco; FMRP-USP = Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo; HUCFF/UFRJ = Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FIPE/HCPA = Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre; RBP = Revista Brasileira de Psiquiatria; ABP = Associação Brasileira de Psiquiatria; UNESCO = United Nations Educational, Scientific and Cultural Organization.
For more information, see Instructions for authors.

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