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Current situation of long-term treatment of depression

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Depression is the most common mental illness and the primary cause of disability. Currently, major depression is considered a chronic disorder, with very high lifetime recurrence rates. This article reviews the published literature on long-term treatment of depression, with special emphasis on unresolved issues of long-term treatment such as prevention of relapses and recurrences and optimal duration of maintenance treatment. Current recommendations on the treatment of major depression include three phases: the acute phase (4-8 weeks), where the objective is to achieve remission; the continuation phase, to maintain remission; and the maintenance phase, to prevent possible recurrences. Most of the studies reviewed support antidepressive therapy during continuation and/or maintenance phases, in patients who have responded to acute and/or continuation treatment with antidepressants. Current scientific evidence suggests that the effect of treatment persists for at least two years of maintenance treatment with antidepressants.

Key words:
Major depressive disorder. Antidepressants. Relapse. Recurrence. Long-term treatment.

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Situación actual del tratamiento a largo plazo de la depresión

La depresión es la más común de las enfermedades mentales y la principal causa de incapacidad. Actualmente se considera que la depresión mayor es un trastorno crónico, con tasas muy elevadas de recurrencia a lo largo de la vida. En el presente artículo se ha realizado una revisión de la literatura publicada sobre el tratamiento a largo plazo de la depresión. Se ha hecho especial hincapié en las cuestiones no resueltas en el tratamiento a largo plazo, la prevención de recaídas y recurrencias y la duración óptima del tratamiento de mantenimiento. Las recomendaciones actuales sobre el tratamiento de la depresión mayor incluyen tres fases: la fase aguda (4-8 semanas), cuyo objetivo es lograr la remisión; la fase de continuación, cuyo objetivo es preservar la remisión, y la fase de mantenimiento, para prevenir las posibles recurrencias. La mayoría de los estudios revisados apoyan el tratamiento con antidepresivos durante las fases de continuación y/o mantenimiento en pacientes que han respondido al tratamiento agudo y/o de continuación con antidepresivos. La evidencia científica actual sugiere que el efecto del tratamiento persiste al menos durante los 2 años de tratamiento de mantenimiento con antidepresivos.

Palabras clave:
Trastorno depresivo mayor. Fármacos antidepresivos. Recaída. Recurrencia. Tratamiento a largo plazo.

INTRODUCTION

Depression is the most common mental illness. It is the main cause of disability (measured in, Years Lived with Disability, or YLDs), and is the fourth most important factor contributing to the global burden of the illness (measured in Disability Adjusted Life Years or DALYs, which is equal to the sum of the years of potential life lost due to an early death and the years of productive life lost due to disability)[1]. In Europe, one in every five persons will suffer from depression during their lifetime[2]. A recent study carried out on a sample of 21,425 persons from six European countries, including Spain showed that major depression was the most common psychiatric disorder: 13% of the study participants claimed to have suffered at least one episode of major depression during their lifetime and 4% during the last year[3].

The approach to diagnosis and treatment of major depression has changed considerably over the years. At the beginning of the 20th century, depression was considered a chronic disorder requiring long-term therapy. During the psychopharmacological revolution of the 1960s and 1970s, major depression was reconsidered as a disorder requiring

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no more than short-term therapy[4]. This stance changed in the 1980s owing to the results of several studies examining the long-term outcome of patients with depression[5]. Since then, major depression has once again been considered a chronic disorder. Patients treated for an episode of major depression present a relapse rate of up to 50% during the first 4-6 months[6], and up to 90% of those who have suffered an episode of major depression will experience a recurrence during their lifetime[6-8]. Furthermore, patients who, after a first depressive episode, continue to present residual symptoms below the diagnostic threshold for depression have been observed to have a significantly worse outcome[9]. Similarly, an increase in the number of episodes is known to reduce the length of symptom-free periods, response to conventional antidepressive agents, and quality of life[10].

These data speak for themselves and show the importance of pharmacological therapy in so far as it attenuates or prevents relapses and/or recurrences.

Table 1 Factors to be considered when starting maintenance therapy

Factor	Component
Risk of recurrence	Number of previous episodes; presence of concomitant psychiatric or medical disorders; residual symptoms between episodes
Severity of the episodes	Suicide risk; psychotic traits; severe functional impairment
Side effects with continued treatment	
Patient preferences	

Adapted from American Psychiatric Association. Practice guidelines for the treatment of patients with major depressive disorder (revision). Am J Psychiatry 2000;157(Suppl.):1-45)[7].

PHASES OF ANTIDEPRESSIVE THERAPY

Findings on the chronic nature of major depression have had an effect on the recommended treatment schedules. In 2000, the American Psychiatric Association (APA) published a series of clinical guidelines for the management of major depressive disorder in adults[7]. These guidelines recommend that antidepressive therapy consists of an acute phase, a continuation phase, and a maintenance phase. The acute treatment phase should last 4-8 weeks and aims to achieve remission of the acute depressive episode. After the success of the acute treatment phase, the same drug should be continued at the same dose for 4 or 5 months more: this phase is known as the continuation phase, and aims to preserve remission. After the continuation phase, and at least six months after the start of therapy, the patient's history will determine whether it is necessary to prolong pharmacological therapy with a maintenance phase to prevent possible recurrences (see table 1 for the factors to be taken into account). All these recommendations are made with the maximum level of clinical confidence (level I, Recommended with substantial clinical confidence). When the guidelines were published, data justifying the importance of continuation and maintenance therapy were based on studies analyzing tricyclic antidepressants (TADs). More recent studies have confirmed the benefits of continuation and maintenance therapy with other classes of antidepressants[11-16].

Nevertheless, current usage patterns of antidepressive agents are very far from following these clearly established guidelines based on clinical evidence[17]. High rates of early withdrawal from therapy in different patient samples have been observed[18-22]. A random sample of 5% of the Medicaid user database in California from 1983 to 1988 (n = 2344) reveals that only 3.5% of patients with depression received an adequate minimum dose of TADs over a six-month period[23]. An analysis of 1648 new episodes of major depression between 1987 and 1996 reveals that only 18% of patients treated with TADs and between 14% and 55% of those treated with selective serotonin reuptake inhibitors (SSRIs) received an adequate dose for at least 6 months[23]. In a recent study of 829 patients who started therapy with antidepressive agents, more than 40% discontinued treatment during the first 30 days[24]. Therefore, the inability to maintain antidepressive therapy at adequate doses for a sufficient period is a common and important cause of failure when trying to achieve remission[17].

REMISSION, RELAPSE, RECURRENCE

Initially, patient response to antidepressants (defined as a 50% improvement compared with baseline values on a depression scale) was considered to be a suitable objective for clinial trials[25]. Several studies have shown that treatment to response only involves an increased risk of relapse, worse psychosocial results, a future lack of response to therapy, and residual disability[26,27]. More recently, remission has become the primary objective in clinical trials[25,28-31]. Remission requires the patient to be asymptomatic and to suffer no more than minimal residual symptoms. Furthermore, there must be a total restoration of the functioning[28,32]. Controlled clinical trials lasting 6-8 weeks with most commercially available antidepressants have shown response rates of between 50% and 75% in major depression[7]. Total remission of symptoms occurs in about 45% of patients treated with venlafaxine and in 35% of those treated with SSRI[30].

Relapse is defined as an episode of major depressive disorder occurring within six months of response or remission

after the initial episode. Recurrence is defined as another depressive episode occurring after 6 months[25]. Nevertheless, several authors have observed that there is no widely accepted definition of recovery, namely, the duration of the remission period necessary to determine whether there is complete recovery from the depressive episode[25,33,34]. In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[35], the term recovery can only be used after at least two months of total remission[36].

It has been suggested that the best strategy for managing possible relapses and recurrences of depression could be prevention by means of long-term pharmacological therapy[25]. In order to prevent relapses during the continuation phase, treatment with the complete dose of the antidepressants that enabled the remission of the acute episode must be prolonged for at least 4-9 months after the acute remission/response. Once this high-risk period has finished, the dose could be reduced gradually in those patients who do not present a high risk of recurrence[25].

INITIAL SELECTION OF ANTIDEPRESSIVE THERAPY

Although the initial drug is increasingly selected depending on tolerability and the lack of side effects, we have already indicated in other publications that the choice of antidepressant should be based on the subtype of depression, following conventional criteria. Therefore, in my opinion, melancholic depression benefits more from TADs and other dual-action antidepressants, whereas non-melancholic depression would respond adequately to SSRIs, dual antidepressants, and new antidepressants[37,38]. By contrast, selection based on the current criteria of major depressive disorder and dysthymia does not show differences between the action of the different antidepressants, because the nosological nuances are imprecise and ambiguous[39,40].

The APA clinical guidelines for the management of major depressive disorder in adults[7] recommend several valid options for the treatment of the acute phase: antidepressive agents, psychotherapy, electroconvulsive therapy (ECT), and the combination of psychotherapy and pharmacological treatment. With regard to the choice of a specific drug, as mentioned above, there are no systematic clinical trial data that compare the efficacy of the different antidepressants with the criterion for major depressive disorder[41]. Therefore, at present, the initial choice of drug is based mainly on the following: expected side effects, safety, or tolerability in a particular patient, patient preferences, the quantity and quality of clinical trial data on the drug, and costs[7]. Thus, the APA believes that the following drugs are usually optimal for most patients: SSRIs, desipramine, nortriptyline, bupropion, and venlafaxine. In general, the monoamine oxidase inhibitors (MAOI) should only be used if there is no response to other therapies, owing to their potential serious side effects and the need for dietary restrictions[7].

REVIEW OF LONG-TERM TREATMENT OF DEPRESSION

The effects of long-term treatment of depression depend on many factors[42], including: *a)* choice of drug; *b)* maintenance dose; *c)* duration of treatment; *d)* somatic status during therapy; *e)* optimization of compliance; *f)* suspension and withdrawal of therapy, and *g)* measures to be taken if the maintenance strategy fails.

Furthermore, methodological shortcomings of most studies involving drugs prevent us from drawing definitive conclusions on the prevention of recurrences[10]. The following are the most important: *a)* small sample size; *b)* lack of control group; *c)* lack of control over the number of previous episodes; *d)* no clear distinction between relapse and recurrence; *e)* sudden suspension of treatment; *f)* duration of study under two years, and *g)* criteria for recurrence that vary from study to study, which makes comparison difficult.

Pharmacological therapy with antidepressants

Several clinical trials with short follow-up periods (8-12 weeks) have evaluated the efficacy of antidepressive agents during the acute phase[43]. There are few studies on long-term therapy (continuation and maintenance) of depression and the prevention of recurrences due to the methodological difficulties described above: the study period must be sufficiently long, adherence must be good, and patients must take their daily dose of antidepressants regardless of their mood[44].

The APA currently recommends that patients treated with antidepressants during the acute phase should continue treatment with the same drug at the same dose during the continuation phase[7]. In general, treatment that has proven effective during the acute and continuation phases should also be used in the maintenance phase at the same dose, since the use of lower doses has not been adequately studied[7]. The traditional controversy over whether to reduce the dose of acute or consolidation therapy was settled by the Pittsburg group[45,46] in favor of high doses, similar to those used for acute treatment. Furthermore, switching to an antidepressant different from that used in the acute episode is only justified in the case of a medical event, side effects that are difficult to manage, or severe drug-drug interactions that warn against continuing with the same drug[10].

In the present article, we review the literature on long-term treatment of depression since August 2000 (studies prior to this period were systematically reviewed by Geddes et al.[47]) until October 2006, using PubMED with the following search terms: long-term treatment; maintenance treatment; continuation treatment; relapse; recurrence; major depression; major depressive disorder; placebo; controlled; randomized; and the names of the individual antidepres-

sants. The article references obtained in the search were reviewed in order to look for other studies on the subject. The only studies reviewed were randomized, double-blind, placebo-controlled studies. To be included, the studies had to have enrolled patients with major depressive disorder who had responded to acute therapy, and the patients had to be randomized to receive therapy with an antidepressant or with placebo for ≥6 months (equivalent at least to the continuation phase).

Twenty studies (table 2) fulfilled the inclusion criteria[14-16,44,48-65]. Of these[14-16,18,44,48,50-65] had positive results; continuation and/or maintenance therapy with antidepressants was significantly more effective than placebo at predicting relapses/recurrences of depression. In one of the studies[63], no significant differences were observed in the proportion of recurrences between the groups treated with an antidepressant (sertraline) and those that received placebo. In another[49], the differences between the probabilities of recurrence with an antidepressant (nefazodone) and with placebo were only significant during the last part of the maintenance period. The follow-up period after randomization was greater than one year in only 8 of the studies[14,48,51,53-55,58,63-65], and the number of patients was very small in two studies[59,61]. In summary, most studies (18 out of a total of 20) support treatment with antidepressants during the continuation and/or maintenance phases in patients who have responded to acute and/or continuation therapy with antidepressants.

The effect of antidepressive therapy persists for at least the two years of maintenance therapy. Three studies have two-year follow-up periods, in which the drug used was venlafaxine extended release, citalopram, and paroxetine[53-55,58]. In the study by Keller et al.[53,54] (1,096 patients), venlafaxine extended release in monotherapy proved efficacious as maintenance treatment for two years in patients with recurrent depression. After two years of maintenance therapy, the probability of accumulated prevention of recurrences with venlafaxine extended release was 72%, compared with the 53% observed with placebo. The study by Klysner et al.[55], included 240 patients with major depressive disorder. Although citalopram proved effective when compared with placebo for preventing recurrence of depression, only 10 patients (6 with citalopram and 4 with placebo) continued with their treatment until the end of the second year; therefore, long-term data should be studied with caution. The paroxetine study[58] included 195 patients who received paroxetine combined (or not) with psychotherapy, with or without augmentation with bupropion, nortriptyline or lithium: when compared with placebo, combination therapy was more efficacious in the prevention of recurrence. Maintenance therapy with imipramine for three years[64] with or without psychotherapy also proved efficacious in the prevention of recurrences in a population of 230 patients diagnosed with recurrent major depressive disorder. Of these, 20 went into an extension phase of an additional two years[65].

These results are similar to those of Geddes et al.[47] in a systematic review of 31 randomized, double-blind, placebo-controlled studies (n=4,410) where the objective was to determine whether continued treatment with antidepressants reduces the risk of relapse or recurrence. Geddes et al., concluded that continuing treatment with antidepressants (as opposed to discontinuing treatment) reduces the risk of relapse by 70% (relapse rate with antidepressants: 18% [465/2,527]; relapse rate with placebo: 41% [1,031/2,505]). The effect of treatment seems to last for three years, although the authors maintain that evidence of the benefits of long term-treatment must be confirmed due to a lack of data.

With regard to the choice of a specific drug, the APA[7] states that there is still not enough information on the comparative efficacy of the different drugs used in long-term therapy. Few studies have compared the long-term efficacy of different antidepressants[13,66], although there is increasing evidence that the SSRI and dual antidepressants, especially venlafaxine extended release, are effective in therapy[53-55,58]. At the time of this review, venlafaxine extended release is the only new-generation antidepressant that has proven efficacious in monotherapy for the prevention of new depressive episodes in patients with recurrent depression during two-year maintenance therapy. Nevertheless, as mentioned above, there are likely to be differences with regard to the response to antidepressants depending on the subtype of depression.

As far as dosing in long-term therapy is concerned, several studies[67-69] have assessed the management of relapses during long-term therapy with antidepressants. The options include restarting therapy with the same drug at the same dose, or increasing the dose[68]. Fava et al.[67], and Schmidt et al.[69], evaluated the response to restarting or increasing the dose of fluoxetine in patients who relapsed in a long-term randomized, double-blind, placebo-controlled study comparing two doses of fluoxetine[60]. The authors conclude that restarting therapy with fluoxetine 20 mg/day[67] was effective for patients who relapsed after interrupting therapy with fluoxetine 20 mg/day. By contrast, patients who relapsed while receiving fluoxetine 20 mg/day benefited from the increase to 40 mg/day, as supported by other studies[69]. The results of these studies support restarting therapy with the same antidepressant in patients who relapse after discontinuing therapy with a previously effective drug[67].

Data on the efficacy of antidepressant combinations are still insufficient[7] and new studies are necessary to determine long-term efficacy[70].

Other therapeutic options

Lithium

Several studies[10] and meta-analyses[71,72] show that lithium is efficacious in preventing relapses and recurrences

Table 2 Randomized, double-blind, placebo-controlled studies on long-term therapy of major depression

Authors (reference)	Participants	Therapy before randomization	Follow-up (months)	Objectives	Relapses/ recurrences with drug. No. (%)	Relapses/ recurrences with placebo. No. (%)	Conclusions
Dalery et al., 2001[48]	111 tianeptine, 74 placebo	6 weeks' open therapy with tianeptine	16.5	Compare the efficacy and acceptability of tianeptine vs. placebo in long-term therapy of recurrent unipolar major depression	18/111 (16.2)	27/74 (36.5)	Relapses and recurrences were significantly more frequent in the placebo group, with no differences in acceptability in both groups
Gelenberg et al., 2003[49]	76 nefazodone, 84 placebo	12 weeks acute therapy with nefazodone ± psychotherapy. Responders receive 16 weeks' continuation therapy	52[a]	Study the efficacy and safety of nefazodone in preventing recurrences in patients suffering from chronic major depressive disorder	20/76 (26.3)	29/84 (34.5)	By applying a competitive risks model to estimate the probability of recurrence in patients who, at the end of the study, were still in treatment, a significant difference was observed between nefazodone and placebo, but only when the last part of the maintenance was emphasized
Gilaberte et al., 2001[50]	70 fluoxetine, 70 placebo	8 weeks' open therapy with fluoxetine; responders receive 32 weeks' continuation therapy with fluoxetine	48[a]	Evaluate the efficacy of therapy with fluoxetine to reduce the number of episodes and increase the symptom-free period in patients with recurrent unipolar major depression	14/70 (20)	28/70 (40.0)	Fluoxetine is significantly more effective than placebo in preventing new episodes of depression in patients with more than one episode during the previous 5 years
Hochstrasser et al., 2001[51]	132 citalopram, 132 placebo	6-9 weeks of open, acute therapy with citalopram; 16 weeks' open continuation therapy	48-77[a]	Compare the efficacy of citalopram with placebo in the prophylaxis of recurrent unipolar depression.	24/132 (22)[b]	59/132 (76.0)[b]	Treatment with citalopram is significantly more effective than placebo for preventing recurrences
Keller et al., 2005[52]	126 gepirone, 124 placebo	8-12 weeks' open therapy with gepirone	40-44[a]	Evaluate the long-term efficacy and tolerability of extended-release gepirone to prevent relapses	29/126 (23)	43/124 (34.7)	The relapse rate was significantly lower in the gepirone group than in the placebo group

Table 2 Randomized, double-blind, placebo-controlled studies on long-term therapy of major depression (continued)

Authors (reference)	Participants	Therapy before randomization	Follow-up (months)	Objectives	Relapses/ recurrences with drug. No. (%)	Relapses/ recurrences with placebo. No. (%)	Conclusions
Keller et al., 2006[c 53,54]	Maintenance phase A: 164 venlafaxine XR, 172 placebo Maintenance phase B: 43 venlafaxine XR, 40 placebo	10 weeks' acute randomized double-blind therapy, venlafaxine XR or fluoxetine. Responders enter a 6-month continuation phase with venlafaxine XR or fluoxetine	24[d]	Evaluate the efficacy and safety of venlafaxine XR in preventing recurrences in patients with recurrent depression	Maintenance phase A: venlafaxine XR (23.1)[e] Maintenance phase B: venlafaxine XR (8)[e] Combined phase 2 years: venlafaxine XR (28.5)[e]	(42)[e] (44.8)[e] (47.3)[e]	The probability of recurrence during the two-year maintenance phase was significantly lower in patients who continued treatment with venlafaxine XR compared with those who were randomized to placebo at the end of each maintenance phase. Treatment with venlafaxine XR was associated with a significantly greater time to recurrence than placebo
Klysner et al., 2002[55]	60 citalopram, 61 placebo	8 weeks' acute therapy with citalopram; in responders, 16 weeks' continuation therapy with citalopram	48-126[a]	Compare the efficacy of citalopram with placebo in prophylaxis of recurrences in elderly patients (over 65 years of age)	19/6 (31,7)[f]	41/61 (67.2)[f]	Long-term treatment with citalopram is significantly more effective than placebo in preventing recurrences in elderly patients who respond to citalopram
Lepine et al., 2004[14]	95 sertraline 50 mg/day, 94 sertraline 100 mg/day, 99 placebo	At least 4 months' open therapy with an antidepressant (except sertraline), 2 months with simple-blind placebo	18	Determine whether sertraline prevents recurrences of major depression in patients with recurrent major depression in remission after therapy with other drugs.	50 mg/day: 16/95 (16.8) 100 mg/day: 16/94 (17)	33/99 (33.3)	In patients with recurrent major depression in remission, sertraline is significantly more effective than placebo at preventing recurrences of major depression
Montgomery et al., 2004[44]	225 (109 venlafaxine, 116 placebo)	Acute and continuation therapy, 6 months, with venlafaxine	12	Study the efficacy of conventional doses of venlafaxine in preventing recurrences of depression in responders.	(22)[e]	(55)[e]	Maintenance therapy with venlafaxine is significantly more effective than placebo at preventing recurrences

Table 2 Randomized, double-blind, placebo-controlled studies on long-term therapy of major depression (continued)

Authors (reference)	Participants	Therapy before randomization	Follow-up (months)	Objectives	Relapses/ recurrences with drug. No. (%)	Relapses/ recurrences with placebo. No. (%)	Conclusions
Perahia et al., 2006[56]	136 duloxetine, 142 placebo	12 weeks' open therapy with duloxetine	26[a]	Evaluate the efficacy, safety, and tolerability of duloxetine in the prevention of relapses of major depression	According to protocol criteria: 23/136 (16.9) According to investigator criteria: 29/136 (21.3)	39/142 (27.5) 59/142 (41.5)	Duloxetine is effective for the prevention of relapses of major depression during continuation therapy
Rapaport et al., 2004[57]	181 escitalopram, 93 placebo	8 weeks' acute randomized, double-blind therapy with escitalopram, citalopram or placebo; 8 weeks' open therapy with flexible doses of escitalopra	42[a]	Evaluate the efficacy and safety of continuation therapy with escitalopram	(26)[e]	(40)[e]	Continuation therapy with escitalopram is significantly more effective than placebo at preventing relapses
Reynolds et al., 2006[58]	28 paroxetine + psychotherapy, 35 paroxetine + clinical management, 35 placebo + psychotherapy, 18 placebo + clinical management	8 weeks' therapy with paroxetine and weekly psychotherapy; in responders, 16 weeks' paroxetine and psychotherapy every 2 weeks, ± bupropion, nortriptyline or lithium	24	Determine the efficacy of maintenance therapy with paroxetine and monthly interpersonal psychotherapy in preventing recurrences of a major depressive episode in patients aged > 70 years	Paroxetine ± psychotherapy: 20/63 (31.7)	Placebo ± psychotherapy: 31/53 (58,5)	In patients aged >70 years with major depression who respond to initial therapy with paroxetine and psychotherapy, two-year maintenance therapy with paroxetine is significantly more effective than placebo at preventing recurrences
Sackeim et al., 2001[59]	27 nortriptyline, 28 nortrptyline + lithium, 29 placebo	Open therapy with ECT	24[a]	Study the efficacy of continuation therapy with nortriptyline or nortriptyline + lithium to prevent post-ECT relapses	Nortriptyline: 15/27 (55.6) Nortriptyline + lithium: 9/28 (32.1)	21/29 (72.4)	With no active treatment, almost all the patients in remission relapse during the first six months post-ECT. Monotherapy with nortriptyline has limited efficacy. The combination of nortriptyline and lithium is more effective, but the relapse rate is high
Schmidt et al., 2000[60]	190 weekly fluoxetine, 189 daily fluoxetine, 122 placebo	13 weeks' open therapy with fluoxetine	25[a]	Study the efficacy and safety of enteric-coated fluoxetine in continuation therapy	125/379 (33.0)	57/122 (46.7)	Daily/weekly fluoxetine is significantly more effective than placebo in preventing relapses of major depression in responders

Table 2 Randomized, double-blind, placebo-controlled studies on long-term therapy of major depression (continued)

Authors (reference)	Participants	Therapy before randomization	Follow-up (months)	Objectives	Relapses/ recurrences with drug. No. (%)	Relapses/ recurrences with placebo. No. (%)	Conclusions
Simon et al., 2004[15]	154 venlafaxine, 138 placebo	8 weeks' acute therapy with venlafaxine XR	6	Evaluate the efficacy of venlafaxine XR in preventing relapses of depression in patients who respond to venlafaxine XR	40/154 (26)	64/138 (46.4)	The accumulated relapse rate calculated by the Kaplan-Meier method was significantly lower in patients treated with venlafaxine XR than in those who received placebo
Thase et al., 2001[16]	76 mirtazapine, 80 placebo	8-12 weeks' open therapy with mirtazapine	40[a]	Evaluate the efficacy and safety of mirtazapine in reducing the risk of relapses of depression	15/76 (19.7)	35/80 (43.8)	The risk of relapse was significantly lower in patients treated with mirtazapine than in those who received placebo
Van der Broek et al., 2006[61]	11 imipramine, 15 placebo	Previous therapy with antidepressants and ECT	6	Compare the efficacy of imipramine and placebo in preventing relapses after ECT in pharmacotherapy resistant depressive patients	2/11 (18.2)	12/15 (80)	The risk of relapse was singificantly lower in patients treated with imipramine than in those who received placebo
Weihs et al., 2002[62]	210 bupropion, 213 placebo	8 weeks' open acute therapy with bupropion	44[a]	Evaluate the safety and efficacy of bupropion in reducing the probability of relapses of depression in patients who responded to bupropion	(37)[e]	(52)[e]	The risk of relapse was significantly lower and the time to relapse was significantly greater in patients treated with bupropion than in those who received placebo
(Wilson et al., 2003[63]	56 sertraline, 57 placebo	8 weeks' open acute therapy and 16-20 weeks' continuation with sertraline	100[a]	Evaluate the efficacy of sertraline in preventing recurrences of depression in elderly patients in the community	25/56 (44.6)	31/57 (54.4)	There were no significant differences in the proportion of recurrences with sertraline and placebo

Table 2 Randomized, double-blind, placebo-controlled studies on long-term therapy of major depression (continued)

Authors (reference)	Participants	Therapy before randomization	Follow-up (months)	Objectives	Relapses/ recurrences with drug. No. (%)	Relapses/ recurrences with placebo. No. (%)	Conclusions
Frank et al., 1990[64]	26 psychotherapy, 26 psychotherapy + placebo, 25 psychotherapy + imipramine, 23 clinical management + placebo, 28 clinical management + imipramine	Open acute therapy and 17 weeks' continuation with imipramine and psychotherapy	36	Evaluate the efficacy of maintenance interpersonal psychotherapy in preventing recurrences of recurrent depression.	Imipramine + psychotherapy: 6/25 (24.0)[e] Imipramine + clinical management: 6/28 (21.4)[e] Psychotherapy: 16/26 (61.5)[e] Imipramine: 1/11 (9.1)[e]	Placebo + clinical management: 18/23 (78.3)[e] Placebo + psychotherapy: 17/26 (65.4)[e] Placebo: 6/9 (66.7)[e]	The risk of recurrences was significantly lower in patients treated with imipramine than in those who received placebo. Monthly interpersonal psychotherapy extended the time between depressive episodes in patients who did not receive active medication
Kupfer et al., 1992[65]	57 placebo		24 (additional)				

[a]Duration of follow-up in weeks. [b]The duration of follow-up was different for patients on citalopram and for those on placebo. For those on citalopram (24/132 recurrences) it was 108.9 person-years, and for the placebo group (59/132 recurrences) it was 77.6 person-years. The raw percentages of recurrences in the table are recurrence rates per person-year. [c]Results available as a poster. [d]Maintenance phase A (12 months): responders to venlafaxine XR, randomized to venlafaxine XR or placebo (placebo group A); responders to fluoxetine continued with fluoxetine; Maintenance phase B (12 months): responders to venlafaxine XR randomized to venlafaxine XR or placebo (placebo group B); responders to placebo (placebo group A) continued with placebo; responders to fluoxetine continued with fluoxetine. Venlafaxine XR: extended-release venlafaxine. [e]Probability of recurrences estimated using survival analysis methods. [f]The duration of follow-up was different for patients on citalopram and for those on placebo. For patients taking citalopram (19/60 recurrences) it was 53.8 person-years, and for the placebo group (41/61 recurrences) it was 30.3 person-years. The percentages of recurrences included in the table are calculated by the authors for week 104 using the Kaplan Meier method, by adjusting for follow-up between both groups.

of unipolar depression, and it is now being questioned whether lithium is more or less effective than antidepressants[10]. In general terms, lithium does not seem to be systematically justified in the maintenance treatment of unipolar depression. However, 10-15% of these patients will develop a manic episode. In these cases, in suspected bipolar cases (periodic cyclical depressions, family history of bipolar disorder, etc.), and in cases in which prevention with antidepressants has proven ineffective, prophylaxis with lithium can be considered[10,73].

Electroconvulsive therapy (ECT)

ECT is one of the most effective treatments for acute-phase depression. However, given the high relapse rate, acute therapy with ECT is usually followed by somatic or psychological therapy during the continuation and maintenance phases[74].

The use of ECT in the continuation phase has received little attention, but it could be useful in patients who have not stabilized during the continuation phase after medication or psychotherapy[7]. According to the APA clinical guidelines[7,11], there is insufficient evidence on the use of ECT in the maintenance phase, and on the optimal duration and frequency of therapy. A recent review supports the use of ECT in continuation and maintenance therapy of depression, but admits that most of the studies reviewed are case reports and retrospective reviews, with very few controlled prospective studies[74].

Psychotherapy

At present, the most common method for preventing relapses/recurrences is continuation/maintenance therapy with antidepressants[47], although it does have some limitations. Not all patients are prepared to take the medication indefinitely and others discontinue prematurely. Sometimes, the drugs are contraindicated due to somatic conditions or side effects[75]. Furthermore, several studies have observed that adherence is usually poor, and that a high percentage of patients with major depression discontinue therapy before six months[23,24]. Moreover, protection against relapses or recurrences ceases once the treatment with antidepressants is over[76]. Some authors have suggested that the high rates of relapse and recurrence in some depressed patients are not due to a lack of adherence or interruption of therapy, but to the intractability of the disorder[77].

Many of those who defend cognitive therapy argue that its protective effect against relapses/recurrences continues long after the end of treatment[78,79]. The results of a recent review support this hypothesis[79].

The APA clinical guidelines[7,11] state that there is evidence that patients who receive cognitive-behavioral therapy during the acute phase have lower relapse rates than those who take antidepressants and later discontinue treatment, and a relapse rate equivalent to that of patients who take antidepressants during the continuation phase[80].

Several studies have shown that cognitive-behavioral therapy could be an effective continuation treatment for preventing relapses after therapy with antidepressants[81-87]. With regard to maintenance therapy, most published studies support the efficacy of psychotherapy with (out) drugs to prevent recurrences[88-90]. The classic study by Frank et al.[46] in Pittsburg showed that a weekly session of interpersonal psychotherapy was more active than placebo but clearly inferior to psychotropics. Similarly, a recent review[77] of seven randomized placebo-controlled studies specially designed to assess the decrease in the risk of relapses and recurrences concluded that cognitive therapy offers significant benefits that last beyond the end of therapy.

In any case, analysis of this area fails to take into account one fundamental aspect; the subtype of depression. In this sense, psychotherapy is likely to be efficacious in non-melancholic depression and to help with adherence to therapy in melancholic depression. Nevertheless, we believe that it has no value in the treatment of melancholia, which responds only to biological therapy, especially TADs and dual-action antidepressants. The failure to take this point into account casts a shadow over the conclusions that can be drawn on this important problem.

Some studies have shown that the combination of psychotherapy and pharmacotherapy has inconsistent results[91-94], although a recent meta-analysis suggests that it is more effective than pharmacotherapy alone[95]. According to the APA clinical guidelines[7,11], combination therapy could be particularly useful for improving adherence[91,95].

Other options

The results of studies on the efficacy of hypericum in acute therapy are inconsistent[11]; there is only one randomized, double-blind, placebo-controlled study on continuation and maintenance therapy[96]. With regard to repetitive transcranial magnetic stimulation, current evidence comes mainly from cases or case series[97], and the APA[11] does not recommend routine use of this technique in clinical practice. In our experience, with data of a study that has not yet been published, the results are poor and patients who improve relapse very quickly.

Limitations

First, this review of long-term therapy with antidepressants cannot rule out the possibility of a publication bias in favor of articles with positive results, since unpublished results were not reviewed. In many cases it is difficult to com-

pare relapse/recurrence rates or the time to relapse/recurrence in the different studies, since they use different criteria to determine the response to therapy, relapse/recurrence, and/or remission. A simple change in the criteria could produce very different results. For example, in the study by Perahia et al.[56], the relapse rate in patients treated with placebo increases from 27.5% to 41.5% if the investigator's criteria are used instead of those of the protocol.

Furthermore, some authors claim that long-term antidepressive therapy is not as effective as believed[98-100], and that it may even exacerbate the course of depression[99].

Unsolved questions

Regarding long-term antidepressive therapy, one of the questions to be solved by future studies concerns the comparative efficacy of the different drugs in continuation and maintenance therapy. Second, studies on the side effects produced by the chronic use of each antidepressant are necessary. Third, the optimal duration for maintenance therapy must be established. Finally, it is necessary to evaluate whether the combination of antidepressants from different pharmacological classes is more effective than monotherapy.

As far as psychotherapy is concerned, more randomized, double-blind, placebo-controlled studies are necessary to determine the efficacy and optimal frequency of psychotherapy sessions in continuation and maintenance therapy, as well as its incidence on each subtype of depression. With regard to ECT, the optimal methodology and indications for using its use in maintenance therapy must be determined.

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