Evidence That Patients With Single Versus Recurrent Depressive Episodes Are Differentially Sensitive to Treatment Discontinuation: A Meta-Analysis of Placebo-Controlled Randomized Trials

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Background: Antidepressants are effective in the prevention of relapse after remission from an acute depressive episode. It is unclear, however, to what degree duration of the continuation phase, level of abruptness of antidepressant discontinuation, or the number of previous episodes moderate the prophylactic effect of antidepressants.

Data Sources: Searches were conducted to identify all published randomized, placebo-controlled, double-blind clinical trials available for review by May 2007 on the efficacy of continuation or maintenance treatment of major depressive disorder with either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) that included patients entering a maintenance phase after achieving remission from the acute phase. The MEDLINE and EMBASE databases were searched using the terms *depression, antidepressants, discontinuation,* and *maintenance treatment*; this was followed by reference checks of articles thus identified. In addition, the Cochrane Library was also searched using the same terms. Some authors of the identified papers were contacted for specific data.

Data Synthesis: Data were collected from 30 trials with 4890 participating patients. The overall reduction of relapse risk in the maintenance phase was highly significant for both SSRIs (OR = 0.24, 95% CI = 0.20 to 0.29) and TCAs (OR = 0.29, 95% CI = 0.23 to 0.38) over 1 year of follow-up of maintenance treatment. The prophylactic effect appeared to be constant over the length of the continuation phase. Recurrent episode patients experienced less protection from antidepressants over the maintenance phase (OR = 0.37, 95% CI = 0.31 to 0.44) than single episode patients (OR = 0.12, 95% CI = 0.06 to 0.26).

Conclusions: Antidepressants robustly reduce relapse risk in the maintenance phase, regardless of a number of clinical and pharmacologic factors. There is evidence, however, that with increasing number of episodes, patients develop a relative resistance against the prophylactic properties of antidepressant medication.

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Depression often manifests itself as a chronic or a recurrent illness; 15% to 20% of depressed patients experience a chronic course, and 75% to 80% of patients experience recurrent episodes.[1,2] Therefore, treatment should focus not only on improving symptoms of the acute episode but also on the prevention of relapse (return of symptoms of the index episode) and recurrence (the development of a subsequent episode).[3] The efficacy of antidepressants in treating acute episodes (4–6 and up to 12 weeks) has been well established in placebo-controlled studies, although the effect sizes for antidepressant treatment are only moderately larger than for placebo.[4,5] Moreover, antidepressants are effective in long-term treatment. In a 2003 meta-analysis of 31 randomized trials (4410 participants), Geddes et al.[6] showed that continuing antidepressant therapy consistently reduced the risk of relapse and recurrence by 70% compared with continuation with placebo, and this seemed to be similar for all classes of antidepressants. They also found no differences in relapse and recurrence rates between patients

with shorter (1–2 months) and longer (4–6 months) treatment after having achieved remission and prior to randomization or between patients with relatively short (6 months) versus longer (up to 36 months) follow-up, suggesting that the reduced risk is largely independent of the duration of treatment before randomization and the duration of the randomly allocated therapy.

Besides the question of how long treatment should be continued once remission has been attained, another important question facing clinicians in their daily practice is, first, to what degree do patients with multiple episodes acquire additional vulnerabilities that could make them more vulnerable not only to discontinuation of the antidepressant per se, but also to the mode of discontinuation (gradual or acute)? The rationale for such a distinction between single and multiple episode patients was proposed by Post and colleagues[7] in an attempt to account for several phenomena observed in the course of affective illness; they emphasized the importance of preventing episodes with prophylactic treatment to inhibit sensitization. According to the sensitization model, a subgroup of patients exists who with each recurrent episode becomes more vulnerable, or "sensitized," to affective episode precipitants. The authors suggested that these patients show characteristics of a sensitization or kindling-like process, in which the biochemical and physiologic processes involved in the illness become progressively more easily triggered by the same circumstances or precipitants compared to the first episode.

Therefore, in the literature on relapse prevention by antidepressants, several questions remain unanswered. It is unclear (1) how long treatment should be continued after remission is achieved (e.g., 6 months, 1 year, longer?), (2) whether treatment should be continued longer in patients with multiple episodes compared to single episodes, and (3) how the antidepressant should be discontinued: can it be done abruptly or within 1 week, or should it be tapered off gradually for 1 or more weeks? In the present study, these questions were addressed, with the hypothesis that multiple episode patients would be more sensitive to antidepressant discontinuation, in particular abrupt discontinuation.

METHOD

In 1988, the MacArthur Foundation Research Network on the Psychobiology of Depression convened a task force to examine the ways in which change points in the course of depressive illness until that time had been described and the extent to which inconsistencies in these descriptions might hinder research on this disorder.[8] Consistent conceptualization and empirical validation of these terms were considered desirable for the following reasons: (1) to be able to improve design, interpretation, and comparison of studies on natural course and treatment; (2) to be able to clarify the relationship between biological and psychological correlates of illness; (3) to create improved guidelines for evaluation of clinical efficacy of drugs and other treatments by regulatory agencies; (4) to be able to conduct empirically based revisions of diagnostic criteria; and (5) to be able to develop improved treatment guidelines for clinical practice. Guided by these statements, the following definitions were constructed.

Definitions

In the literature, the terms *response*, *remission*, *relapse*, and *recurrence* and the terms describing the different treatment phases (*acute treatment*, *continuation treatment*, and *maintenance treatment*) are not uniformly defined. In this article, the definitions by Frank and colleagues[8] were followed. The first phase in treatment is acute treatment, aimed at the suppression of the depressive symptoms. Response is defined as a clinically significant reduction of symptoms of depression (e.g., at least 50% reduction of the score on the Hamilton Rating Scale for Depression [HAM-D]), and remission is defined as the remaining of no or only minimal symptoms of depression (e.g., a score of less than 9 points on the HAM-D). During the first 6 months after remission is achieved, the underlying illness may still be present and discontinuation of the treatment can cause reappearance of symptoms of the original episode; this is called a relapse. In this context, *continuation treatment* is the term applied to the prevention of a relapse, i.e., the treatment phase during the first 6 months after having achieved remission. After these 6 months of remission, the underlying disorder is considered resolved, and when a new depressive episode appears after this period, it is called recurrence. The term *maintenance treatment* is applied for a treatment with antidepressants that aims at the prevention of a recurrence.

Types of Studies

We wished to identify all published randomized, placebo-controlled, double-blind clinical trials available for review by May 2007 on the efficacy of continuation or maintenance treatment of major depressive disorder with either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) (the 2 groups of comparable and widely used antidepressants with the largest number of trials) in patients who had achieved remission during acute treatment with these antidepressants.

Search Strategy for Identification of Studies

A MEDLINE and EMBASE computerized search using the terms *depression*, *antidepressants*, *discontinuation*, and *maintenance treatment* was conducted and was supplemented with references cited in reports so identified (reference checking). In addition, the Cochrane Library was also searched using the same terms. Some authors of the identified papers were contacted for specific data.

Types of Participants

Trials were eligible for the review if they included patients with major depressive disorder, single or recurrent episode, who were treated with an antidepressant (SSRI or TCA) until remission was attained. These patients had then to be followed up during the continuation and subsequent maintenance phases.

Types of Interventions

Patients obtaining remission and entering the continuation or the maintenance phase had to be randomly divided into at least 2 groups, with at least 1 group receiving active treatment with an antidepressant (SSRI or TCA) and another group receiving placebo, under double-blind conditions.

Data Selection

The search results and the data extracted from the trial reports on participant characteristics, intervention details, and outcome measures were checked by 2 reviewers (N.K. and A.J.M.L.) before analyses. When specific data were not given in the report, the authors were contacted; some authors responded to the 2 efforts we made to contact them, and some did not.

Data were entered into the STATA, version 9, software program (StataCorp, 2005)[9] for further analyses.

Methodological Quality of Included Studies

The assessment of the methodological quality of the trials was carried out by 2 reviewers (N.K. and A.J.M.L.) who used the same checklist. The most crucial aspects of the included trials for the internal validity were (1) the method of randomization and achievement of a double-blind condition and (2) the reporting of withdrawals and dropout rates and use of a suitable survival analysis.

Data Aggregation

The following data were extracted and tabulated from each paper (see Table 1): number of previous episodes, duration of active treatment, duration of stabilization/continuation treatment, number of subjects, duration of follow-up, and duration of withdrawal of medication. Besides these tabulated data, the numbers of individuals at risk over each follow-up interval (at 3, 6, 9, and 12 months) were extracted from the publications whenever they were mentioned or, if they were not, from the survival curves in these publications.

Data Analysis

Data from the selected randomized controlled trials were combined to estimate the pooled odds ratio (OR) with 95% confidence intervals (CIs) using a random-effects model. The presence of heterogeneity across trials was evaluated using a χ^2 test for homogeneity, testing whether individual trials results varied more than could be explained by chance alone. When significant heterogeneity was found, possible causes were explored. In addition, meta-regression was used to assess the degree to which important clinical and study quality factors impacted on the meta-analytic results. Meta-regression extends a random-effects meta-analysis to estimate the extent to which 1 or more covariates, with values defined for each study in the analysis, explain heterogeneity in the treatment effects. In meta-regression, the log odds ratio, representing the antidepressant effect size, is regressed on the variables that are hypothesized to explain heterogeneity in the treatment effects.

Potential publication bias was tested for using Begg's test for asymmetry.

As to the question of effectiveness of continuation and maintenance treatment with antidepressants, relapse/recurrence rates after randomization to either continuation of the antidepressant or switch to placebo were compared, whenever possible, over a 1-year follow-up period separately at 3, 6, 9, and 12 months. If relapse/recurrence rates at these assessment points were not presented in the results of the publication, they were calculated when possible, e.g., by estimating these rates from the survival curves that were presented as figures in most of the publications. The effect of time at follow-up on relapse/recurrence rates was examined using meta-regression analysis with time at follow-up (3, 6, 9, or 12 months) as independent variable and the log odds ratio representing antidepressant effect size as the dependent variable. In order to compile the dataset for this analysis, each study with data (i.e., number of relapses/recurrences) at 3, 6, 9, and 12 months was separated into 4 different studies of 3 months' duration each with the variable "time" denoting whether follow-up was at 3, 6, 9, or 12 months. This way, the effect of time on relapse rate could be assessed in the meta-regression of the effect sizes, using the STATA meta-regression routine in STATA (StataCorp, 2005, version 9).[9] Using this dataset, controlling for time, meta-regression was also applied to investigate whether duration of continuation treatment, after achievement of remission, was associated with the risk of relapse/recurrence after discontinuation of antidepressants. To this end, studies were subdivided according to the duration of continuation treatment prior to randomization as follows: less than 1 month, 1 to 3 months, > 3 to 6 months, and > 6 months (i.e., beyond the continuation phase of 6 months recommended by the guidelines).

Similarly, meta-regression, controlling for time, was used to examine whether mode of discontinuation in controlled studies affected relapse rates by comparing abrupt discontinuation (< 1 week) with gradual discontinuation (tapering for ≥ 1 week).

Finally, meta-regression, controlling for time, was used to assess whether clinical features such as the number of previous episodes moderated relapse rates. To this end, the studies were subdivided further into those involving

patients with no previous episode of depression versus those involving patients with multiple episodes, i.e., at least 1 previous episode prior to the index episode. As we had hypothesized that the patients most sensitive to the antidepressant discontinuation would be those with the combination of multiple episodes and an abrupt mode of discontinuation, a number of previous episodes–by–mode of discontinuation interaction term was fitted in the meta-regression model.

In the event that a variable in the meta-regression was found to impact significantly on the meta-analytic result, separate meta-analyses were carried out for the different strata of this variable, so as to clarify the direction and magnitude of group differences in effect size.

A test for selection bias was carried out, visualizing the included studies in a Begg's funnel plot with pseudo 95% confidence limits.

RESULTS

Identified Studies

The search process yielded 44 studies possibly satisfying the inclusion criteria, i.e., the continuation/maintenance treatment was with either an SSRI or a TCA. Fourteen studies were excluded due to methodological limitations: 1 because the study was single blind,[10] 4 because there was no placebo control group,[11–14] 1 because the antidepressant in the acute or continuation phase was not the same antidepressant as in the maintenance phase,[15] 4 because lithium was added during the acute phase to achieve remission,[16–19] 1 because the study was not formally published,[20] and 1 because patients with bipolar disorder were also included.[21] We also excluded 1 study[22] of maintenance treatment with a 5-year follow-up as it included patients who were also part of the 3-year maintenance study by Frank et al.[45] One study (McGrath et al.[23]) was excluded as it did not mention the number of relapses separately for the medication and placebo arms in this study. Only the active treatment arms, without crossover, and the placebo arm of the studies with different assignment groups in which relapse rates are mentioned separately for the different arms of the study were included.

The characteristics of the 30 studies included in this meta-analysis are listed in Table 1.[24–53] Some of the studies were 4-armed or 5-armed studies, in which medication was compared to psychotherapy or their combination; from these studies, we only included data from the medication arm and the placebo arm. The 30 trials involved a total of 4890 patients, performed in both primary and secondary care settings, and described 2749 patients who continued with the antidepressant and 2141 patients who were switched to placebo. Fifteen studies were found in which the allocated drug was an SSRI, with a total of 2984 patients, and 15 studies were found in which the allocated drug was a TCA, with a total of 1906 patients. There were no 3-arm studies with 2 medication arms (e.g., both an SSRI and a TCA) versus placebo.

Duration of Continuation Phase

In order to examine the impact of the prerandomization period (e.g., the duration of the continuation phase), studies were divided in 4 subgroups with a duration of less than 1 month, 1 to 3 months, > 3 to 6 months of continuation phase, and > 6 months of continuation plus maintenance phase.

In the subgroup of trials with a continuation treatment of less than 1 month (i.e., remission achieved for less than 1 month) prior to randomization, 9 trials (1261 patients in total) were found, and of these, 7 trials (954 patients) provided information at 3 months of follow-up, 6 trials (727 patients) provided information at 6 months of follow-up, 3 trials (339 patients) provided information at 9 months of follow-up, and 2 trials (101 patients) provided information at 12 months of follow-up. In the subgroup of trials with 1 to 3 months of continuation treatment prior to randomization, 2 trials (95 patients) provided information at 3 (85 patients), 6 (70 patients), 9 (63 patients), and 12 (59 patients) months of follow-up. In the subgroup of trials with > 3 to 6 months of continuation treatment prior to randomization, 17 trials (3194 patients in total) were found, and of these 17 trials, 14 (2384 patients) provided information at 3 months of follow-up, 13 trials (2104 patients) at 6 months of follow-up, 11 trials (1846 patients) at 9 months of follow-up, and 9 trials (1547 patients) at 12 months of follow-up. Only 1 study was found (Bialos et al.[38]) with a clearly mentioned treatment period prior to randomization of more than 6 months. Another study, by Cook et al.,[42] had a duration of 52 weeks, but did not clarify how long the duration of the acute and continuation treatment lasted. These publications were included in the subgroup of studies with a prerandomization period of 3 to 6 months. To examine the impact of time at follow-up (3, 6, 9, and 12 months) on relapse/recurrence rates, we have used meta-regression analysis on pooled results of 30 trials in total (4890 patients) (see Figure 2), 23 trials (3441 patients) providing information at 3 months of follow-up (see Figure 3), 21 trials (2914 patients) at 6 months of follow-up (see Figure 4), 16 trials (2259 patients) at 9 months of follow-up (see Figure 5), and 8 trials (1710 patients) at 12 months of follow-up (see Figure 6).

Number of Previous Depressive Episodes

With regard to the number of episodes prior to the index period, 4 trials (301 participants) included patients with no prior episodes, and 17 trials (2939 participants) included patients with at least 1 episode prior to the index episode. The remaining 9 studies of the total of 30 were left out of the analysis, because some studies included both single- and recurrent episode patients. Some studies

Table 1. Characteristics of the Included Studies

Study	Diagnosis	Diagnostic Criteria	No. of Previous Episodes	Duration of Active Treatment Phase (wk)
Montgomery et al, 1988[24]	MDD	DSM-III	≥ 2	6
Doogan and Caillard, 1992[25]	MDD	DSM-III-R	Not reported	8
Montgomery and Rasmussen, 1992[26]	MDD	DSM-III-R	Not reported	6
Montgomery and Dunbar, 1993[27]	MDD	DSM-III-R	≥ 2	8
Robert and Montgomery, 1995[28]	MDD	DSM-III-R	≥ 2	8
Keller et al, 1998[29]	Chronic depression, MDD, double depression[a]	DSM-III-R, HAM-D	Mixed	12
Reimherr et al, 1998[30]	MDD	DSM-III-R	Not reported	12–14
Terra and Montgomery, 1998[31]	MDD	DSM-III-R	≥ 2	6
Hochstrasser et al, 2001[32]	MDD	DSM-IV	≥ 2	6–9
Klysner et al, 2002[33]	MDD	DSM-IV	0	8
Mindham et al, 1972[34]	Depression	MRC	Not reported	3–10
Klerman et al, 1974[35]	Depression	DSM-II	0	4–6
Coppen et al, 1978[36]	Depression	MRC	11 patients = 0; 21 patients ≥ 1	Not reported
Stein et al, 1980[37]	MDD	Feighner[b]	≥ 1	6
Bialos et al, 1982[38]	Depression	RDC	Chronic depression	Not reported
Kane et al, 1982[39]	Depression	RDC	≥ 2	Not reported
Glen et al, 1984[40]	Depression	MRC	0	Average 8½
Prien et al, 1984[41]	Depression	RDC	≥ 1	Not reported
Cook et al, 1986[42]	MDD	RDC	≥ 1	Not reported
Georgotas et al, 1989[43]	MDD	RDC	≥ 3	7–9
Rouillon et al, 1989[44]	MDD	DSM-III	≥ 1	8
Frank et al, 1990[45]	Depression	RDC	≥ 2	Not reported
OADIG, 1993[46]	MDD	RDC	50% = 1; 50% ≥ 1	16
Reynolds et al, 1999[47]	MDD	RDC	Average 5	Not reported
Alexopoulos et al, 2000[48]	MDD	RDC, DSM-IV	Most = 1 or > 2	Not reported
Wilson et al, 2003[49]	MDD	DSM-III-R, HAM-D	0	8
Gilaberte et al, 2001[50]	MDD	DSM-III-R	≥ 1	8
Schmidt et al, 2000[51]	MDD	DSM-IV	Mixed	13
McGrath et al, 2006[52]	MDD	DSM-IV	Chronic depression	12
Perahia et al, 2006[53]	MDD	DSM-IV	≥ 1	12

[a]Major depression with antecedent dysthymic disorder.
[b]Feighner et al. 1972 criteria.
Abbreviations: CGI = Clinical Global Impressions scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale,

included only patients with a chronic depressive disorder or did not specify the number of previous episodes.

Mode of Discontinuation of the Antidepressant

Antidepressant medication was discontinued abruptly (< 1 week) in 22 trials (4320 participants) and gradually (≥ 1 week) in 8 trials (630 participants). No studies were found that included both abrupt and gradual discontinuation.

Publication Bias

The distribution of effect size–related measures relative to sample size–related measures did not suggest publication bias in the studies used for this meta-analysis (Figure 1).

Treatment Effects

Overall, the results showed that continuing antidepressant therapy consistently reduced the risk of relapse (OR = 0.30, 95% CI = 0.25 to 0.35, $p < .001$) compared to placebo (Figure 2), with no significant heterogeneity detected ($\chi^2 = 40.21$, df = 29, $p = .081$). This effect was highly significant for SSRIs (OR = 0.24, 95% CI = 0.20 to 0.29, $p < .001$) as well as for TCAs (OR = 0.29, 95% CI = 0.23 to 0.38, $p < .001$).

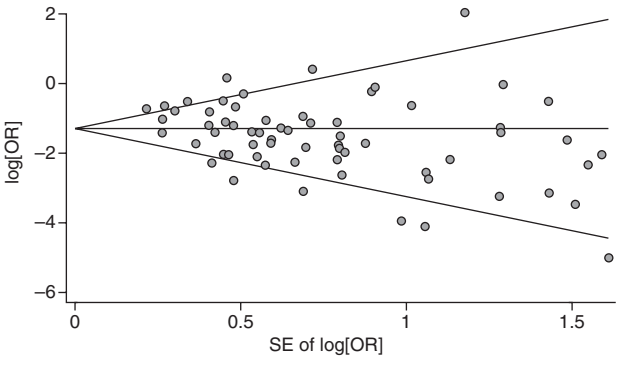
Using meta-regression, the overall relapse-reducing effects of the SSRIs were not significantly different from those of the TCAs (meta-regression coefficient = –0.30, 95% CI = –0.78 to 0.17, $p = .209$). However, it should be noted that none of the studies involved (next to placebo) a head-to-head comparison of TCAs versus SSRIs.

Duration of Stabilization/ Continuation Phase (prerandomization phase) (wk)	No. of Patients in Trial	Criteria for Relapse/Recurrence	Duration of Follow-Up (mo)	Withdrawal of Medication (wk)
24	Fluoxetine = 88, placebo = 94	HAM-D > 18	12	< 1
0	Sertraline = 185, placebo = 110	Clinical criteria, CGI ≥ 4	11	3
0	Citalopram = 105, placebo = 42	MADRS ≥ 22	6	< 1
0	Paroxetine = 68, placebo = 67	CGI ≥ 4, clinical criteria	12	< 1
0	Citalopram = 152, placebo = 74	MADRS ≥ 25, clinical criteria	6	< 1
16	Sertraline = 77, placebo = 84	DSM-III criteria for at least 3 wk, CGI ≥ 4, HAM-D ≥ 4 points higher than maintenance phase baseline	19	Maximum 3
0	Fluoxetine = 102, placebo = 96	HAM-D ≥ 14 for 3 successive wk, DSM criteria for minimum 2 wk	12½	< 1
18	Fluvoxamine = 109, placebo = 94	Clinical criteria	12	< 1
16	Citalopram = 132, placebo = 132	MADRS ≥ 22 confirmed at 3–7 d, CGI ≥ 5	12–19	< 1
16	Citalopram = 60, placebo = 61	MADRS ≥ 22	12	< 1
0	Amitriptyline = 50, placebo = 42	Clinical criteria on monthly screenings	6	< 1
0	Amitriptyline = 25, placebo = 25	Clinical criteria	8	< 1
6	Amitriptyline = 16, placebo = 16	Increase in symptoms sufficient to warrant hospital admission	12	< 1
2	Amitriptyline = 28, placebo = 27	Clinical criteria	6	< 1
192	Amitriptyline = 7, placebo = 10	Clinical criteria	6	3
24	Imipramine = 6, placebo = 6	RDC, clinical criteria	24	< 1
0	Amitriptyline = 8, placebo = 9	Clinical criteria	36	2
Not reported	Imipramine = 39, placebo = 34	RDC, GAS ≤ 60, clinical criteria	24	< 1
≥ 52	TCA = 6, placebo = 9	Clinical criteria	8	4–8
16	Nortriptyline = 13, placebo = 23	RDC, HAM-D ≥ 16	12	< 1
24	Maprotiline = 767, placebo = 374	MADRS > 27 or > 25 for 2 wk	12	< 1
17	Imipramine = 28, placebo = 23	RDC, HAM-D ≥ 15, Raskin ≥ 7	36	< 1
8	Dothiepin = 33, placebo = 36	MADRS >10, clinical criteria	24	< 1
16	Nortriptyline = 28, placebo = 29	RDC	36	6
16	Nortriptyline = 22, placebo = 21	RDC, DSM-IV criteria, HAM-D ≥ 17	24	10
16–20	Sertraline = 56, placebo = 57	HAM-D ≥ 13, DSM-III-R clinical criteria	24	< 1
24	Fluoxetine = 70, placebo = 70	HAM-D ≥ 18, CGI ≥ 4, DSM-III-R	12	< 1
Not reported	Fluoxetine = 189, placebo = 122	Criteria for depressive episode determined by the SCID-P, CGI-S ≥ 2	25	< 1
24	Fluoxetine = 131, placebo = 131	2 wk of ratings of less than "much improved" on the CGI, compared with ratings at study entry	8	< 1
24	Duloxetine = 136, placebo = 142	CGI ≥ 2 compared to baseline, MINI criteria for MDD	½	1

Abbreviations continued: MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Interview, MRC = U.K. Medical Research Council, OADIG = Old Age Depression Interest Group, Raskin = Raskin Depression Scale, RDC = Research Diagnostic Criteria, SCID-P = Structured Clinical Interview for DSM-IV patient version, TCA = tricyclic antidepressant.

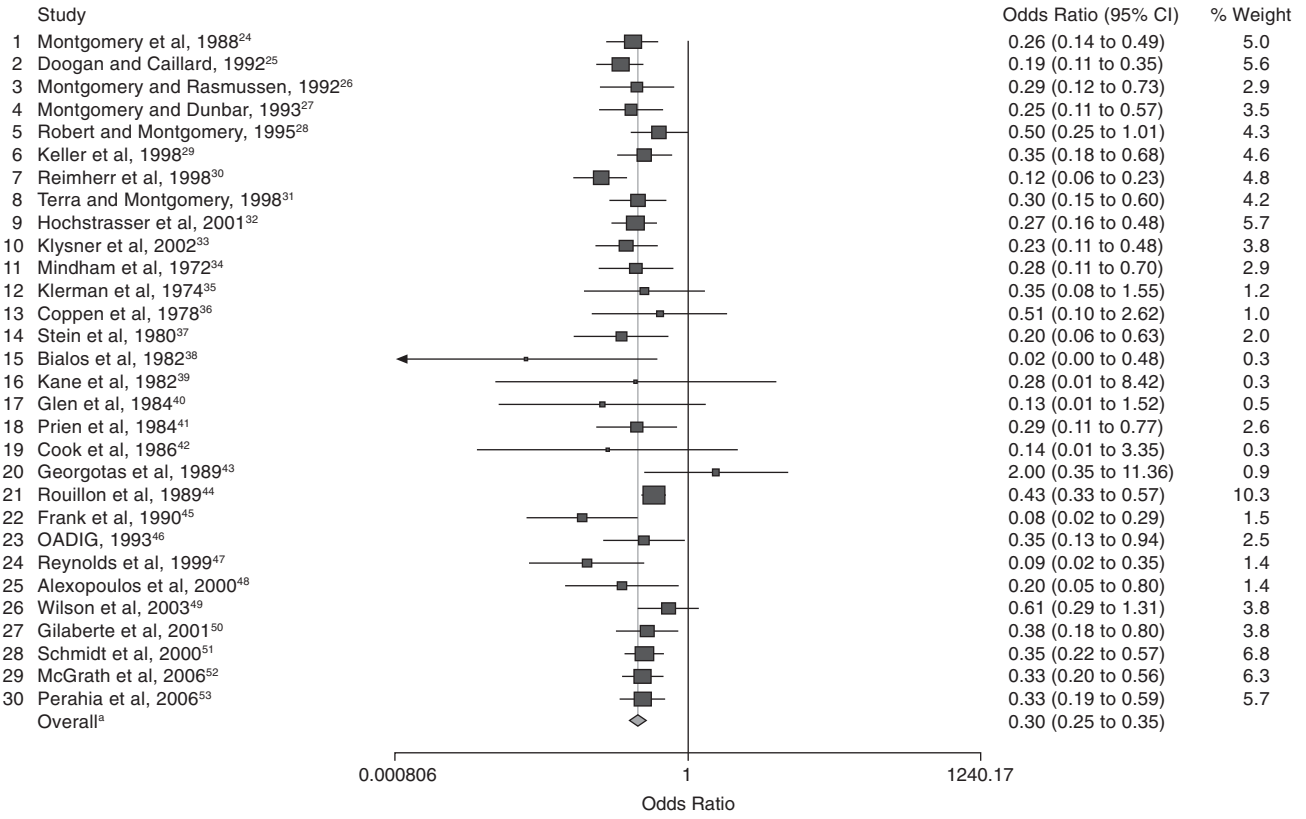
Comparing the relapse rates as a function of time at follow-up revealed that antidepressants at 3 months of follow-up significantly reduced relapse rates compared to placebo (OR = 0.25, 95% CI = 0.17 to 0.36, p < .001) (Figure 3). At further follow-up, this remained unchanged at 6 months (OR = 0.19, 95% CI = 0.13 to 0.29, p < .001), at 9 months (OR = 0.29, 95% CI = 0.21 to 0.40, p < .001), and at 12 months (OR = 0.27, 95% CI = 0.12 to 0.60, p = .001) (Figures 4–6). Meta-regression confirmed this result: with longer follow-up, there was no significant additive relapse-reducing effect, neither at 6 months compared to the first 3 months (meta-regression coefficient = –0.24, 95% CI = –0.77 to 0.28, p = .367), nor at 9 months compared to the first 3 months (meta-regression coefficient = 0.14, 95% CI = –0.44 to 0.72, p = .635),

Figure 1. Begg's Funnel Plot With Pseudo 95% Confidence Limits



Abbreviation: OR = odds ratio.

Figure 2. Recurrence in the Antidepressant and Placebo Groups in the Pooled Analysis of All Included Studies



[a]Pooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

nor at 12 months compared to the first 3 months (meta-regression coefficient = 0.10, 95% CI = –0.65 to 0.85, p = .790).

Duration of Continuation Phase

In meta-regression, the prerandomization periods of 1 to 3 months and of > 3 to 6 months after achievement of remission showed no significantly different relapse-reducing effect of the antidepressant compared to a pre-randomization treatment period of less than 1 month (meta-regression coefficient = 0.41, 95% CI = –0.73 to 1.57, p = .478 and meta-regression coefficient = 0.20, 95% CI = –0.26 to 0.68, p = .389, respectively).

Number of Previous Depressive Episodes

The meta-regression comparing patients with recurrent episode(s) versus those with a single episode revealed a significant positive regression coefficient, indicating less antidepressant benefit for patients with recurrent episodes (meta-regression coefficient = 1.6, 95% CI = 0.60 to 2.59, p = .002). Meta-analyses stratified for this variable revealed that the pooled OR for relapse in single episode patients was considerably lower (OR = 0.12, 95% CI = 0.06 to 0.26, p < .001), without significant heterogeneity (χ^2 = 10.79, df = 7, p = .148), compared to the OR for relapse in recurrent episode patients (OR = 0.37, 95% CI = 0.31 to 0.44, p < .001), also without significant heterogeneity (χ^2 = 23.15, df = 22, p = .393).

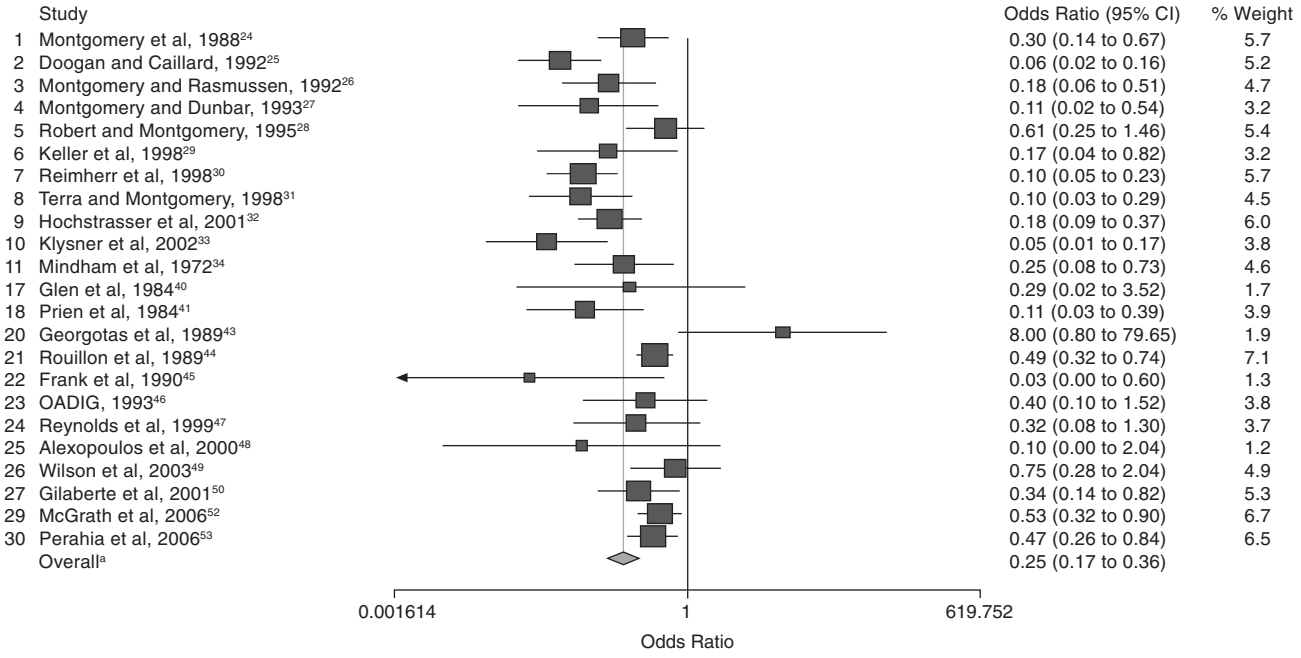
Mode of Discontinuation of the Antidepressant

With regard to the question of possible moderation of the effect size of antidepressant as a function of mode of discontinuation of the antidepressant, it was found that the relapse rates in studies with gradual discontinuation of the antidepressant (i.e., ≥ 1 week) were not different from those in studies with abrupt discontinuation (i.e., < 1 week) (meta-regression coefficient = –0.56, 95% CI = –1.37 to 0.24, p = .174).

Interaction Between the Number of Previous Episodes and Mode of Discontinuation of the Antidepressant

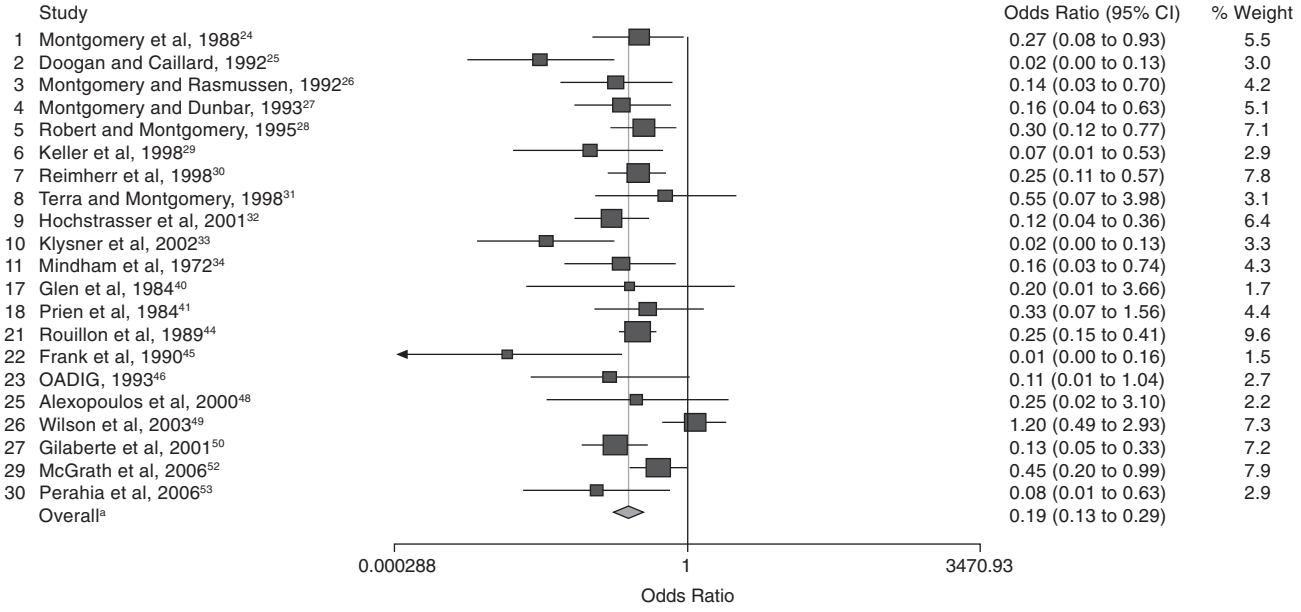
In the meta-regression, there was a significant positive interaction between the variables number of previous episodes and mode of discontinuation (meta-regression coefficient = 2.15, 95% CI = 1.01 to 3.29, p < .001). Thus, in the recurrent episode patients, abrupt discontinuation was

Figure 3. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 3 Months of Follow-Up in the Maintenance Treatment



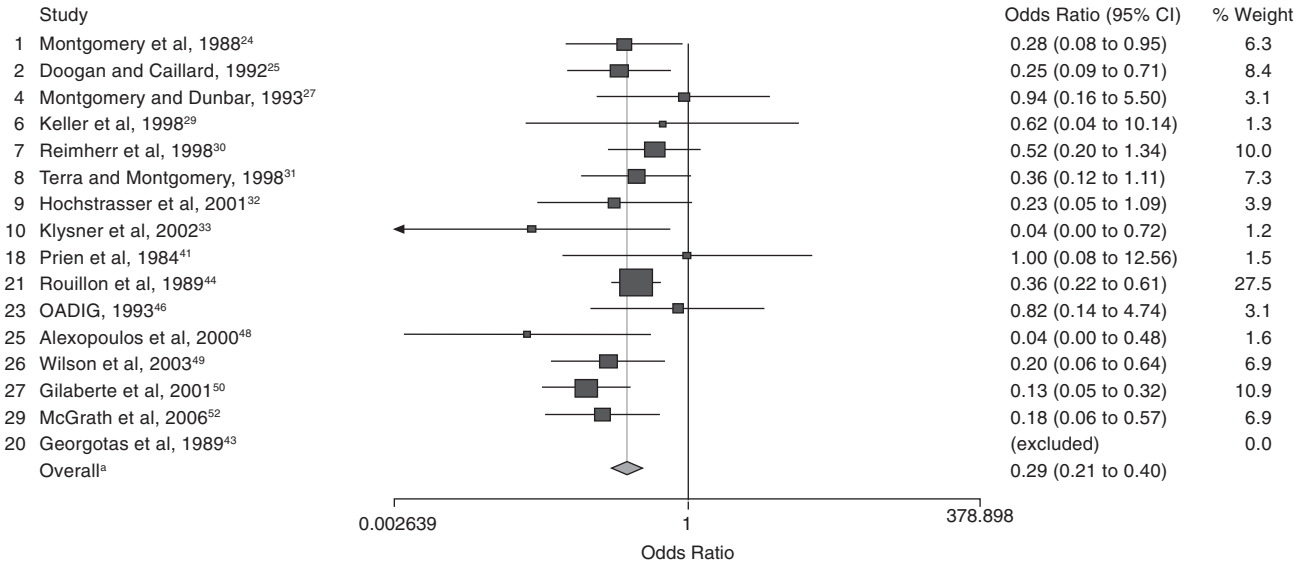
[a]Pooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

Figure 4. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 6 Months of Follow-Up in the Maintenance Treatment



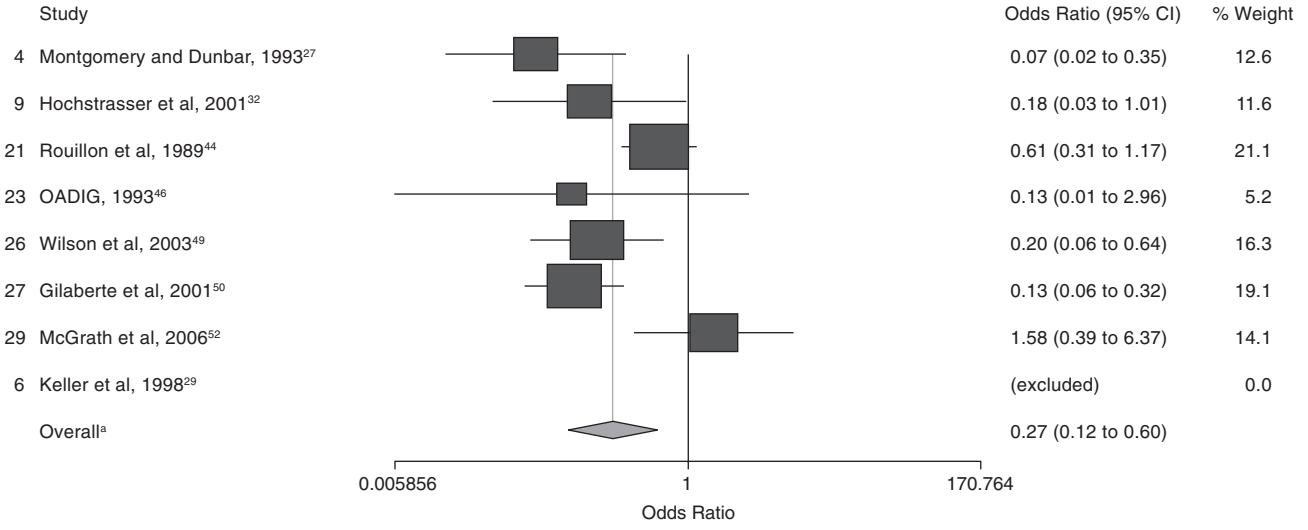
[a]Pooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

Figure 5. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 9 Months of Follow-Up in the Maintenance Treatment



[a]Pooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

Figure 6. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 12 Months of Follow-Up in the Maintenance Treatment



[a]Pooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

associated with a lower relapsing preventive effect of antidepressants (OR = 0.32, 95% CI = 0.27 to 0.38, p < .001; heterogeneity: $\chi^2 = 57.20$, df = 41, p = .048), compared to multiple episode patients with gradual discontinuation (OR = 0.11, 95% CI = 0.06 to 0.21, p < .001; heterogeneity: $\chi^2 = 8.30$, df = 9, p = .504), with nonoverlapping confidence intervals of the ORs in the 2 groups. In single episode patients, no such large difference was apparent, and confidence intervals were largely overlapping (abrupt: OR = 0.10, 95% CI = 0.03 to 0.28, p < .001; gradual: OR = 0.19, 95% CI = 0.04 to 0.87, p = .032). The significant heterogeneity in the meta-analysis of recurrent episode patients with abrupt discontinuation was largely due to 1 small study with an unusually large effect size in

the opposite direction (Robert and Montgomery[28]). This study has a meta-analytic weight of less than 1%; therefore, excluding it has little impact on the effect size (but does reduce heterogeneity). Exclusion of this study from the analysis reduced heterogeneity ($\chi^2 = 46.00$, df = 39, p = .205; OR = 0.32, 95% CI = 0.27 to 0.37, p < .001).

DISCUSSION

On the basis of the pooled results of 30 randomized clinical trials, it can be concluded that treatment with an antidepressant results in an approximately 70% reduction of risk of relapse. Thus, the current study confirms the effectiveness of continuation treatment with antidepressants once remission has been achieved, as was reported in previous meta-analyses by Loonen et al.,[3] Geddes et al.,[6] and Viguera et al.[54] In agreement with the latter 2 meta-analyses, it was found that the difference between active medication and placebo was not greater in the studies with SSRIs compared to the studies with TCAs. However, it should be emphasized that no studies were found in which SSRIs and TCAs were compared head-to-head with each other.

In this meta-analysis, several additional questions concerning the continuation and maintenance treatment of depressive disorder were addressed.

Duration of Continuation Phase

Regarding the first question (of how long treatment with antidepressants should be continued once remission has been attained), no significant difference was found between studies with patients who were randomized within 1 month after having achieved remission compared to those in which patients were randomized after a continuation treatment of 1 to 3 months or after 3 to 6 months. This is in line with the results of previous meta-analyses[6,54] that also did not find a difference in relapse rates in relation to the duration of the stabilization prior to discontinuation of the antidepressant.

In answering the question of how long antidepressants should be continued, another perspective can be gained from the comparison of relapse/recurrence rates over the follow-up at 3, 6, 9, and 12 months after randomization. We found significant relapse-reducing effects of antidepressants compared to placebo at 3, 6, and 9 months as well as 12 months of follow-up. However, the difference between antidepressant and placebo was already achieved within 3 months after randomization, with no additional reduction in risk at 6, 9, and 12 months compared to the effect already obtained during the previous periods (up to 3, 6, and 9 months, respectively).

Unfortunately, it was not possible to include studies in which patients were randomized during maintenance treatment, i.e., more than 6 months after remission was achieved. The only available data are from 2 small studies. The first was by Bialos et al.,[38] who studied 17 patients who had been receiving long-term amitriptyline treatment. Eight of 10 patients who had their medication tapered and discontinued had a relapse within 4 months compared to none of the 7 control subjects during the 6 months of the study. The second small study was by Cook et al.,[42] who studied 15 patients who had been receiving a long-term treatment with a tricyclic antidepressant agent. None of the 9 patients who continued on active medication experienced a relapse, whereas 3 of the 9 patients switched to placebo experienced a relapse. With the exception of these small studies, no other studies have specifically addressed the question of whether treatment with antidepressants should be continued longer than 6 months after remission is achieved.

On the basis of the above data taken together, it is not possible to give recommendations for an optimal duration of continuation and maintenance treatment with antidepressants. In fact, there is also no evidence from the reviewed studies of the effect of discontinuation of antidepressants to justify the defined distinction between continuation treatment (up to 6 months) and maintenance treatment (beyond 6 months).

Number of Previous Depressive Episodes

A history of severe and frequently recurring depressive episodes is considered to be a plausible clinical predictor of increased risk of relapse or recurrences after discontinuation of the antidepressant.[22,26,55]

Regarding the second question (of whether treatment should be continued longer in patients with recurrent episodes than in patients who have suffered from a first or second episode), it was found that the reduction in relapse rates was greater for recurrent episode patients compared to single episode patients. In fact, the results support previous findings that patients with 1 or more previous depressive episodes have significantly less benefit from the relapse-reducing effect of the antidepressant than patients with a first episode.[29,54,56] Thus, the results suggest that with longer duration of illness, the risk of relapse is more difficult to control, conforming to the sensitization hypothesis proposed by Post et al.[7] In addition, the data showed that the reduction in the protective effect of antidepressants was specifically evident in the subgroup of patients in which the antidepressant was discontinued abruptly. Post et al. hypothesized that stress of a particular type, intensity, and intermittency may produce sensitization in a fashion similar to the behavioral sensitization. Even in cases of anticipated stresses or imagined losses, if sufficiently conditioned, the behavioral, physiologic, and biochemical alterations usually associated with an affective episode might be produced. It may also explain how stress-induced mood alterations might become so sensitized that they also occur spontaneously. However, it should also be emphasized that it was not possible to

specifically address the question of whether maintenance treatment is especially indicated for patients with recurrent depression, again because there are no studies in which patients were randomized more than 6 months after having achieved remission.

Mode of Discontinuation of the Antidepressant

Regarding the third question (of how quickly the antidepressant should be discontinued), it was found that relapse rates in studies in which patients did discontinue medication abruptly (i.e., < 1 week) were not different from rates in studies in which patients gradually discontinued their antidepressant (i.e., ≥ 1 week), but that instead mode of discontinuation was relevant only for the particular subgroup of recurrent episode patients. This subgroup effect quite likely explains why Viguera et al.[54] found that relapse rates off medication did not differ significantly between studies involving rapid discontinuation and those in which tapering was more gradual for the total group of different types of antidepressants that they included, as the interaction with number of previous episodes was not investigated in that study. Differential distribution of recurrent episode patients may explain why Geddes and colleagues[6] reported an excess of relapse immediately following discontinuation of the antidepressant in the first month of drug discontinuation. Thus, when the interaction with recurrent episode patients is modeled, there is clear evidence that acute withdrawal of medication might induce a relapse, a problem that has also been identified for lithium, for which acute withdrawal can lead to manic relapses,[57–60] and antipsychotics, for which a higher risk of psychotic relapse was found within 6 months of discontinuation, particularly in hospitalized patients and patients in whom the antipsychotics were withdrawn abruptly.[61]

Other Factors

One of the possible mechanisms for the high relapse rates in the first 3 months of randomization may be associated with differences in the half-lives of the various antidepressant agents,[62,63] assuming that the shorter the half-life of the antidepressant, the greater the risk of relapse. However, addressing this question with adequate precision was not possible, since the range of half-lives of the antidepressants used in the different studies is extremely heterogeneous and in addition imprecise, given a great level of interindividual variation, depending on whether the patient is a fast or a slow metabolizer and depending on gender- and age-specific aspects of the elimination of the antidepressant.

Consequences

Several guidelines on the treatment of patients with depressive disorder have addressed the issue of long-term treatment with antidepressants: continuation treatment during the first 6 months after achievement of remission and maintenance treatment thereafter. We looked at the different guidelines and compared the recommendations with the findings of this study.

The recommendations in most guidelines[64–67] stating that patients should be treated for at least 6 months after having achieved remission, and especially that patients with frequent/more previous episodes should receive maintenance treatment, cannot be supported on the basis of the current findings. More specifically, any recommendation about maintenance treatment is not evidence based, due to the fact that studies in which patients were randomized more than 6 months after having achieved remission are lacking. The ORs reported in this article indicate that gradual discontinuation leads to more relapse than abrupt discontinuation. However, it is not possible to differentiate to what extent the smaller OR for single episode studies (OR = 0.12) than for recurrent episode studies (OR = 0.36) can be explained by more relapse with placebo in single episode studies or by less relapse with antidepressant medication in single episode studies. Further investigation of the above mentioned possible pathways for smaller ORs is warranted before firm conclusions can be drawn. Furthermore, in the group of patients with recurrent depressive episodes, those with abrupt discontinuation of the antidepressant appeared to benefit less from the relapse-reducing effect of the antidepressant (OR = 0.32) than those with gradual discontinuation (OR = 0.11). The interpretation of this finding is that since the relapse rate during continuing treatment with an antidepressant should not be different in these studies, the ORs can arguably only be taken to indicate that gradual discontinuation leads to more relapse in placebo groups than abrupt discontinuation. This is a somewhat counterintuitive finding and suggests that findings resulting from models including interaction terms may be due to chance. Furthermore, gradual withdrawal can be recommended in order to prevent other withdrawal symptoms.[68–70]

Another issue is how to perform continuation or maintenance treatment. Some studies detailing the management of a relapse or a recurrence point out that patients who did relapse in the continuation phase after initially having responded to an antidepressant can benefit from an increase in the dose of the same antidepressant or from an increase using an enteric-coated antidepressant initially dosed once a week to twice a week.[71,53,63] In the case of a recurrence after the discontinuation of medication in the maintenance phase, patients can benefit from a reinstatement of the antidepressant. We did not address these aspects in our meta-analysis.

Limitations

The results of our study should be seen in the light of several methodological limitations.

Several reports did not specify certain relevant details, such as the specific antidepressant studied (some reports

just mentioned TCA), doses of the antidepressant, the illness history and more specifically the precise number of previous depressive episodes, the precise duration of treatment after achievement of remission and prior to randomization, and in some studies the mode of discontinuation of the antidepressant. Diagnostic criteria varied, and some studies included an unspecified number of patients with other disorders such as a depression in the course of bipolar II disorder, dysthymia, atypical depression/depression not otherwise specified, or a major depressive episode with a significant comorbid disorder. When relevant details could not be retrieved, the studies were excluded from the subanalyses.

Definitions of remission as well as of relapse/recurrence usually varied between the studies from formal definitions including clinical assessment with application of diagnostic criteria or the use of rating scales, to more global criteria such as worsening of depressive symptoms severe enough to warrant hospitalization or reinstitution of antidepressant treatment. Therefore, it remained unclear in some studies to what degree patients actually had attained full remission prior to randomization and/or to what degree they indeed suffered from a relapse or recurrence of a formal major depressive episode.

The trials were also heterogeneous in terms of diagnostic criteria, dropout rates, the power at the start of the trial, drugs used, and outcome criteria (Table 1). Although the main meta-analytic result did not display significant heterogeneity, the p value was close to .05, suggesting underlying sources of variance. Some of these factors were most likely identified in the meta-regression, in particular the number of previous depressive episodes and the interaction of this variable with mode of discontinuation. Further exploration of other potential variables contributing to heterogeneity, such as age, gender, year of publication, or drug regimen, was not possible due to the limitations inherent to all meta-analyses performed without access to individual patient data, and potential differences between trials in the definition and validation of end points as well as the clinical characteristics of the randomized patients.

Most of the patients participating in the trials consisted of patients in secondary care settings with a more severe and often recurrent type of depressive disorder and thus a high risk of relapse. Patients with milder depressive disorders, such as patients treated in primary care, were underrepresented, so that we can make no inference about the generalizability of our results to this group of patients.

Whether the relapse rates can be explained by the degree of resistance in patients participating in the different studies remains unclear, since the degree of resistance to therapy, prior to participation, was not mentioned in the studies included.

Another limitation is that our results may be subject to publication bias as negative trials are more likely to remain unpublished.[72] This is a general limitation of any conclusion based on perusal of the literature. Using a Begg's funnel plot, however, it was found that there was symmetry in the relationship between effect size and sample size (see Figure 1), with only a slight overrepresentation of small studies with a positive result.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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