Key Words: response, remission, antidepressants, serotonin, tricyclic antidepressants, norepinephrine, venlafaxine, SSRI, SNRI

New Goals in the Treatment of Depression: Moving Toward Recovery

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ABSTRACT *~ Depression is associated with marked suffering, morbidity, and high risk of recurrence and/or chronicity. As a result, the disorder represents a considerable public health problem and economic burden on society. Treatment of patients with depression to a state of remission is associated with a significantly improved long-term outcome, including a reduced risk of relapse and improved functioning. Thus, remission (which can be defined as attainment of a total score ≤7 on the Hamilton Rating Scale for Depression) should be the goal of the acute phase of pharmacotherapy. Although it is widely assumed that available antidepressants are comparably effective, comparisons of the efficacy of antidepressants in clinical trials are flawed by a number of factors. Most notable problems are higher-than-expected placebo effects and low statistical power. Double-blind, comparative studies are also compromised by relatively high attrition rates and the often underestimated effects of patient nonadherence. Large study groups (in the order of 300 patients per treatment group) are needed to differentiate between a good and a potentially better antidepressant. The statistical technique of meta-analysis has been used to examine the results of studies of various antidepressants; these meta-analyses have shown that the selective serotonin reuptake inhibitors (SSRIs) have overall "within group" comparability and, overall, an efficacy profile comparable to the previous standard, tricyclic antidepressants (TCAs). However, in studies of hospitalized patients, TCAs affecting both serotonergic and noradrenergic systems (eg, amitriptyline or clomipramine) have been found to have greater efficacy when compared with SSRIs. Results of some individual studies, as well as a pooled analysis of the outcomes of more than 2,000 depressed patients, indicate that venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor, may have a similar advantage relative to SSRIs across a broader range of patients. These findings suggest antidepressants that affect both serotonergic and noradrenergic neurotransmission may be more likely to accomplish the goal of remission. Compared with TCAs, the better safety profile of venlafaxine has established the drug as a more appropriate first-line treatment option.* Psychopharmacology Bulletin. *2002;36(Suppl 2):24-35*

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INTRODUCTION

The recognition of depression as the world's fourth greatest public health problem[1] underscores the continuing need to develop safe and, if possible, more effective antidepressant agents. A wide range of antidepressant medications is already available, although none can be considered ideal. For example, 40% to 50% of patients who respond to treatment do not achieve remission within the first 6–8 weeks of therapy,[2] which places these patients at a particularly high risk of relapse and a potentially chronic course of illness.[3,4] The functional performance of patients is improved significantly when remission is achieved during acute therapy.[5] Remission and subsequent prevention of relapse or recurrence should be viewed as the gateway to long-term recovery and restoration of a patient's social functioning.

The issue of whether different classes of antidepressants vary with respect to response or remission rates has been a thorny research question. The application of newer quantitative techniques, including meta-analysis and pooled analysis of original data, can help to circumvent the problems associated with individual studies. This article will review research that compares the effects of different antidepressant agents on response and remission rates, emphasizing research using such quantitative methods. A guiding hypothesis is that antidepressants acting on multiple neurotransmitter systems will have greater efficacy, if tolerability is comparable.

THE BURDEN OF DEPRESSION

Depressive disorder is highly prevalent (lifetime United States prevalence=17%) and associated with significant morbidity and mortality (Keller, pages 36-48).[6,7] The economic costs associated with the incidence of depression are considerable. Estimates based on data from 1990 suggest that the annual loss of $44 billion in the US could be attributed to depression, with the majority of these costs (55%) resulting from disability and impaired performance in the workplace.[8] Other significant contributory factors to the economic costs of this condition are inpatient care (19%), suicide (17%), outpatient care (6%), and pharmaceutical costs (3%). Indeed, the World Health Organization Global Burden of Disease Study concluded that not only was depression a leading cause of disability, but it was the fourth most costly of all medical illnesses worldwide and predicted to rank second by the year 2010.[1] Continuing treatment for depression until the patient enters remission lessens the risk of relapse and recurrence, and, thus, reduces lifetime risk of suicide. This represents an important strategy that can reduce the profound suffering and economic burden associated with depression.

Treating to Response Versus Remission

The best way to determine whether a promising new antidepressant medication is effective is to perform a series of double-blind, parallel group, placebo-controlled, randomized clinical trials. In such trials, a response has typically been defined as a ≥50% decrease from baseline total score using the Hamilton Rating Scale for Depression (HAM-D)[9] or Montgomery-Åsberg Depression Rating Scale (MÅDRS),[10] or attainment of a Clinical Global Improvement (CGI) score of 1 or 2. Thus, a response does not represent a full resolution of symptoms, and many patients defined as responders still experience numerous depressive symptoms and impaired functioning. For patients with severe depression, for example, a 50% decrease from baseline HAM-D score would equate to a score still representative of mild-moderate depression. Nevertheless, this convention has been adequate for the task of establishing whether a new antidepressant is better than a placebo.

At both conceptual and pragmatic levels, remission has been viewed as a "higher grade" of response. For example, according to cancer literature, a remission may be viewed as a virtual absence of illness activity. For research purposes, remission has been defined by a reduction of a HAM-D total score to ≤7, at which a patient is essentially asymptomatic and is usually able to resume normal psychosocial and occupational functioning.[11,12] Using this definition, studies have validated that remission is associated with a significant reduction in the psychosocial and economic burdens described above[5] and a substantially lower risk of relapse.[3,13]

Demonstrating Differences Between Antidepressant Agents

The conventional wisdom is that the antidepressant medications that have gained regulatory approval have comparable efficacy in placebo-controlled, double-blind clinical trials. However, this conclusion may be based on flawed data because very few clinical trials actually have sufficient statistical power to differentiate between the efficacy of useful antidepressants. Statistical power refers to the likelihood of detecting a true difference, if one is present. Additionally, the outcome measure of response is relatively easy to achieve, particularly given the remarkably high placebo-response rates observed in some studies of major depression. Approximately 50% of industry-funded studies of novel antidepressants fail to demonstrate significant drug-placebo differences.[14,15] An outcome measure that is more difficult to achieve (ie, remission) may be more likely to demonstrate differential efficacy between two active agents where one is superior.[16] Furthermore, it is statistically more difficult to demonstrate that two agents are not significantly different

from each other (ie, superiority) than it is to show a notable difference between an active antidepressant and a placebo, because of an expected smaller difference.[17] Consequently, the sample sizes of active comparator studies need to be at least twice those that only include a placebo control group, in order to have sufficient power to show statistically significant changes (Table).

Trial results may be further influenced by inconsistencies in the assessment of patients during the study. Even in optimal circumstances the diagnosis of major depressive disorder is made with only 90% interrater agreement. Similarly, the test-retest reliability of measures such as the HAM-D or MÅDRS seldom exceeds the 80% to 90% range. Hence, variability is introduced into the measurement of effects. Most studies also have not included measures of wellness, such as quality of life or work productivity scales. Therefore, a study comparing two effective treatments might be limited further by the so-called "ceiling effect," where there is a narrow range for demonstrating a difference between agents.

No single clinical study of antidepressants is definitive. Some of the difficulties associated with showing meaningful differences between agents in single trials are overcome by the use of meta-analyses. If the differential effect between treatments is relatively modest but consistently observed, the summation of such small effects across a number of studies increases the chances of documenting that a difference is reliable (ie, statistically significant). The major limitations of conventional meta-analyses are twofold. First, if there are only a handful of relevant studies, there is not much statistical power. Only large, consistent effects can be confirmed. Second, a meta-analysis of published studies may be biased if there is a substantial number of negative (ie, drug=placebo), unpublished studies left behind in the "file drawer."

TABLE

PATIENT NUMBERS REQUIRED IN A COMPARATOR TRIAL TO DETERMINE A STATISTICALLY SIGNIFICANT DIFFERENCE IN RESPONSE RATE BETWEEN TWO ACTIVE ANTIDEPRESSANTS

Predicted Difference in Response Rate (Drug 1 vs Drug 2)	*Number of Patients Needed Per Group** (Drug 1)	(Drug 1)
60% vs 30%	62	62
60% vs 40%	N/A	N/A
60% vs 50%	538	538
60% vs 55%	2,092	2,092

* The sample size necessary to achieve 80% statistical power (α=.05, two-tailed χ^2 test).
NA=not available.

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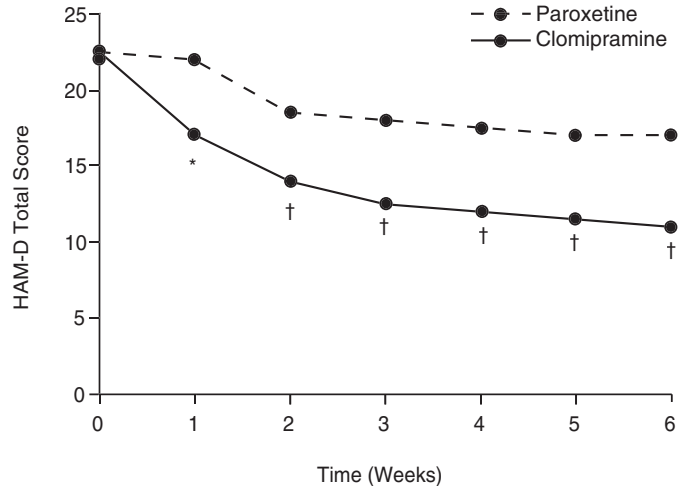
COMPARISON OF THE EFFICACY OF SSRIs VERSUS TCAs

Since the early 1990s, SSRIs have largely replaced TCAs on the basis of safety, ease of use, and day-to-day tolerability. The efficacy of SSRIs and TCAs in the treatment of depression has been examined by a meta-analysis of 62 randomized, controlled trials to assess response and treatment discontinuation rates.[18] This analysis showed no overall differences between various SSRIs and that, as a class, these agents were as effective as TCAs in the treatment of depression, at least as measured in discontinuations for treatment failure. Furthermore, the meta-analysis confirmed that SSRIs were better tolerated than TCAs. These findings have been verified in subsequent, updated meta-analyses.[19,20] However, a sub-group analysis suggested that treatment with TCAs resulted in better outcomes for inpatients, who have generally severe depressive episodes.[21] The greater efficacy of TCAs was attributable to the results of individual studies using TCAs, such as clomipramine and amitriptyline (which inhibit both serotonin and norepinephrine reuptake), and was not apparent in studies using predominantly noradrenergic TCAs, such as desipramine, or the tetracyclic compound, maprotiline.[21] Although few studies reported remission rates, both trials conducted by the Danish University Antidepressant Group found a significant advantage in remission rates favoring clomipramine over citalopram[22] and paroxetine (Figure 1).[23]

FIGURE 1

HAM-D TOTAL SCORES DETERMINED FOR PATIENTS WITH MAJOR DEPRESSION BEFORE AND DURING 6 WEEKS OF TREATMENT WITH PAROXETINE 30 MG/DAY (N=56) OR CLOMIPRAMINE 150 MG/DAY (N=46)



* P=.05 † $P \leq .01$ versus paroxetine
HAM-D=Hamilton Rating Scale for Depression.
Adapted from: Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled, multicenter study. *J Affect Disord*. 1990;18:289-299.

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EVIDENCE FOR DUAL REUPTAKE INHIBITION AS EFFECTIVE THERAPY FOR DEPRESSION

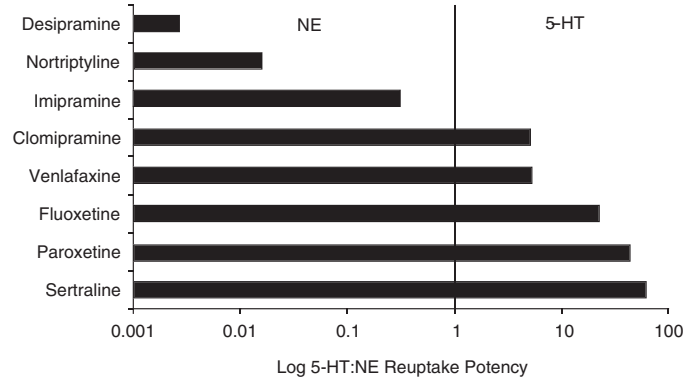
As noted above, the most straightforward explanation for the benefit provided by clomipramine or amitriptyline (but not by desipramine or maprotiline), compared with SSRIs, is the effect on both the serotonin and norepinephrine systems. Although amitriptyline and clomipramine exert relatively weak inhibition of the reuptake of norepinephrine in experimental models (Figure 2),[24] both drugs are rapidly metabolized to strongly noradrenergic compounds (ie, nortriptyline and desmethylclomipramine, respectively). The evidence of differential efficacy only in inpatient studies is usually attributed to illness severity (ie, more severely depressed patients are more likely to manifest objective signs of noradrenergic dysfunction),[25] although it is also true that an inpatient setting would offer better management of TCA adverse events (eg, nursing support, availability of laxatives, and more frequent measurement of blood pressure).

If there is an advantage for "dual" reuptake inhibition, this effect could result from a broader spectrum of efficacy or synergistic effect on neuronal systems. This latter possibility is supported by some preclinical and clinical data. Postsynaptic β-adrenoceptor downregulation is a consistent long-term effect of most antidepressants, although less

FIGURE 2

THE RELATIVE IN VITRO POTENCY OF SELECTED ANTIDEPRESSANTS AS INHIBITORS OF NE AND 5-HT REUPTAKE

The line drawn at value 1 indicates equipotent inhibition of 5-HT and NE reuptake. A medication must have a potent effect on NE and/or 5-HT to be plotted using this scale. Medications that have extremely weak effects on both NE and 5-HT should not be classified according to this ratio scale.



NE=norepinephrine; 5-HT=serotonin.
Adapted from: Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. *Mayo Clin Proc*. 1994;69:1069-1081.

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consistent data have been reported on the influence of SSRIs on β-adrenoceptor density and function.[26-28] The cerebral cortical β-adrenoceptor density of rats was assessed following administration of fluoxetine, desipramine, or a combination of these agents.[28] Combined inhibition of serotonin and norepinephrine reuptake was associated with a faster and more enhanced downregulation of β-adrenergic receptors, as the serotonin and norepinephrine systems are interactive (Nemeroff, pages 6-23) and simultaneous intervention in both systems appears to result in an enhanced effect.

Changes in clinical practice patterns over the past decade provide indirect evidence of additive effects for combining serotonergic and noradrenergic drugs. Not long ago, routine prescription of two different antidepressants ("polypharmacy") was an anathema; today it is considered a standard treatment option for patients who have failed to respond to an SSRI.[29]

Although there are surprisingly few data from randomized, controlled trials that support such wide use of antidepressant combinations, an open clinical study provided interesting preliminary evidence.[30] Combined administration of desipramine and fluoxetine was assessed in inpatients with a diagnosis of major depression, and the data were compared retrospectively with that obtained from an earlier group of inpatients treated only with desipramine. The combination of agents was associated with a significantly faster and more complete response than that achieved with desipramine alone. For patients treated with combined fluoxetine and desipramine, the reduction in HAM-D total score after 1 week of treatment (42%) was significantly greater than that attained in patients receiving desipramine alone (20%). This rapid effect could not be explained by the now well-known pharmacokinetic interaction between these compounds, attributable to fluoxetine-mediated inhibition of desipramine metabolism via hepatic cytochrome P450 (CYP) 2D6.[31] After 4 weeks, 71% of patients receiving both drugs remitted (change in HAM-D score of >75% and total score <7), compared with just 14% of patients receiving only desipramine.

SNRIs in the Treatment of Depression

The potential for improved antidepressant efficacy resulting from dual uptake inhibition has been assessed by comparing the efficacy of the serotonin norepinephrine reuptake inhibitor venlafaxine and SSRIs in the treatment of depression. However, it is likely that this large difference also involved the metabolic interaction, as patients in the combined treatment group had significantly higher desipramine plasma levels. Like

clomipramine, venlafaxine is a relatively more potent serotonin reuptake inhibitor (Figure 2).[24] Venlafaxine has an adverse-event tolerability profile more comparable to SSRIs than TCAs. Moreover, venlafaxine is not highly protein bound (as such, more "free" drug is available to pass through the blood-brain barrier), and it can safely be used in doses as high as 375 mg/day.

More so than any other new antidepressant, venlafaxine has been studied extensively in comparison with various SSRIs. These individual studies are subject to the same methodologic limitations described earlier, and not surprisingly, have yielded mixed results. Some trials have reported unequivocal, statistically significant differences,[32,33] others have reported inconsistent differences across outcome measures,[34-36] and still others have found equivalent outcomes.[37,38]

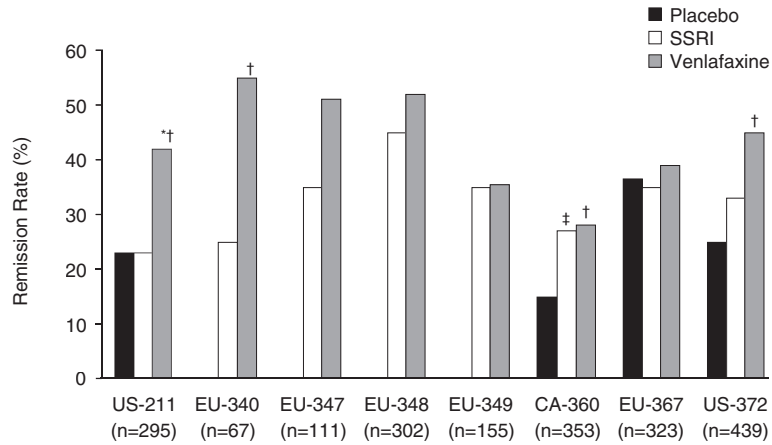
The problem of inconsistent results has been addressed in the first group of eight studies using a pooled analysis of all original data from individual studies. This method offers greater statistical power in detecting differences between active agents when there are only a small number of studies because the unit of observation is the patient, not the number of studies. The initial report examined the original data of 2,045 patients, who were randomly assigned to treatment with venlafaxine, SSRI, or placebo for treatment of major depressive disorder.[16]

Pooled analysis was carried out on data obtained from three 6-week studies and five studies of at least 8 weeks' duration. Four studies were placebo-controlled, and seven of the eight studies were conducted with outpatients. The SSRIs used as comparators were fluoxetine (five studies), paroxetine (two studies), and fluvoxamine (one study), at doses of 20–80 mg/day, 20–40 mg/day, and 100–200 mg/day, respectively. Five studies used the immediate release (IR) formulation of venlafaxine; three evaluated the newer extended release (XR) formulation. The modal dose of venlafaxine used across the studies was 150 mg/day (range: 75–375 mg/day).

In the eight individual studies, the remission rate during venlafaxine treatment was statistically superior to that of SSRI treatment in only two trials (Figure 3). However, the overall remission rates determined from the pooled analysis showed highly significant differences in the proportion of patients in remission during treatment with venlafaxine (45%), as compared with either SSRI (35%), or placebo (25% [Figure 4]). The advantage favoring venlafaxine therapy was sustained irrespective of the definition of remission that was applied, including 17-item HAM-D total scores (≤7 or ≤10) and 21-item HAM-D total scores (≤7, ≤8, or ≤10), ≤50% decrease in HAM-D score, MADRS total score (<10), combined HAM-D total score (≤10), and CGI rating (equal to 1; Figure 4).[16] Examination of temporal trends indicates that the advantage of venlafaxine (relative to SSRIs) was faster remission by about 1 week.

FIGURE 3

REMISSION RATES DETERMINED IN EIGHT INDIVIDUAL STUDIES FOLLOWING 6 WEEKS' (EU-340, EU-347, US-372) OR 8 WEEKS' ADMINISTRATION OF PLACEBO, SSRI, OR VENLAFAXINE IN THE TREATMENT OF DEPRESSION



*$P \leq .05$ venlafaxine versus SSRI.
†$P \leq .05$ venlafaxine versus placebo.
‡$P \leq .05$ SSRI versus placebo.
SSRI=selective serotonin reuptake inhibitor.

Adapted from: Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.

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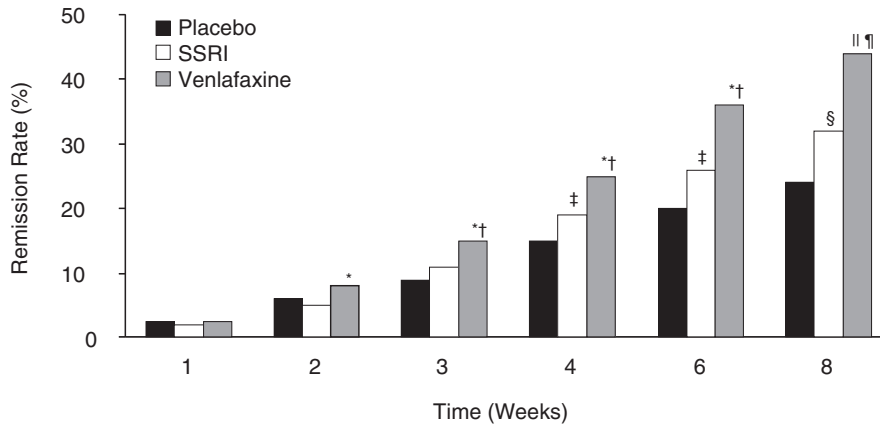
FIGURE 4

REMISSION RATE DETERMINED FROM POOLED ANALYSIS OF STUDIES COMPARING PLACEBO, SSRI, OR VENLAFAXINE IN THE TREATMENT OF DEPRESSION



* $P \leq .05$ venlafaxine versus SSRI.
† $P \leq .05$ venlafaxine versus placebo.
‡ $P \leq .05$ SSRI versus placebo.
§ $P < .001$ SSRI versus placebo.
|| $P < .001$ venlafaxine versus SSRI.
¶ $P < .001$ venlafaxine versus placebo.

SSRI=selective serotonin reputake inhibitor

Source: Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241. Reprinted with permission of the Royal College of Psychiatrists.

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The greater efficacy of venlafaxine was apparent irrespective of study type. For example, remission rates were significantly greater, whether venlafaxine XR or venlafaxine IR formulations were used. Therefore, although studies of venlafaxine IR permitted the use of high doses (ie, up to 375 mg/day), the advantage of venlafaxine was also observed in the studies using the more narrowly recommended dose range of venlafaxine XR (75–225 mg/day).[16] Similarly, the benefit of venlafaxine was demonstrated after excluding the one inpatient study and when the comparison was limited to the five fluoxetine studies.[16] Only in the studies not using a placebo was the effect of venlafaxine not significantly greater than that of SSRIs (ie, P=.06).

Beyond the eight studies included in the pooled analysis, nine other published studies comparing venlafaxine and SSRIs were tabulated by Thase and colleagues.[16] The original data from these additional studies were not yet available for inclusion in the pooled analysis. A second meta-analysis will be needed to examine further the comparative effects of SSRIs and venlafaxine. A qualitative review of these additional studies revealed that the magnitude of effect favoring this dual reuptake inhibitor relative to SSRIs was similar to that observed in the pooled analysis: a 12% difference in response/remission rates.[16]

Conclusion

Remission is the desired outcome of the acute phase of antidepressant therapy. The evidence reviewed indicates that there may be differences in efficacy across the different classes of antidepressant agents available to treat patients with major depression. In addition to the long-recognized differences in tolerability, it is likely that the various proposed mechanisms of action of antidepressants are related to the probability of remission. Moreover, when tolerability is comparable, therapy with medications that work through multiple mechanisms of action appear to result in higher remission rates. It will be of great importance to public health to determine whether these differences, observed in well-controlled clinical studies, generalize to the broader population of depressed patients treated in day-to-day practice. ✤

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