Lamotrigine as Adjunct to Paroxetine in Acute Depression: A Placebo-Controlled, Double-Blind Study

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Background: Mood stabilizers appear to be more potent in treating mania than depression. The anticonvulsant lamotrigine has been shown to be effective for bipolar depression. This study examines putative antidepressive properties of lamotrigine in a mainly unipolar routine clinical patient population.

Method: Forty patients with a depressive episode (DSM-IV criteria) requiring psychiatric intervention received lamotrigine or placebo using a fixed dose escalation scheme with a target dose of 200 mg/day for 9 weeks. Additionally, all patients were treated with paroxetine. Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions scale (CGI) ratings were used to monitor therapeutic efficacy.

Results: Adjunctive treatment with lamotrigine did not result in a significant difference in HAM-D total score at the endpoint of the study when compared with paroxetine alone. However, lamotrigine demonstrated significant efficacy on core depressive symptoms as reflected by HAM-D items 1 (depressed mood; $p = .0019$), 2 (guilt feelings; $p = .0011$), and 7 (work and interest; $p = .049$) and the CGI-Severity of Illness scale ($p < .0001$). Patients receiving lamotrigine had fewer days on treatment with benzodiazepines and fewer withdrawals for treatment failure. Lamotrigine appeared to accelerate the onset of action of the antidepressant. Two patients on lamotrigine treatment developed neutropenia, and 1 developed a benign rash. There was no detectable pharmacokinetic interaction between lamotrigine and paroxetine.

Conclusion: Lamotrigine might have antidepressive properties in unipolar patients and may accelerate onset of action when given in combination with typical antidepressants.

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The treatment of acute depression is the weakest element in the spectrum of efficacy of mood stabilizers.[1] Their acute and prophylactic antimanic properties have been repeatedly shown in controlled studies.[2] In the last few years, there have been a number of clinical trials examining treatment and prophylaxis of bipolar depression; this condition is especially hard to treat, as it involves a high level of treatment resistance and a substantial risk of a switch to mania and the induction of rapid cycling.[3,4] Mood stabilizers are used as first-line treatment of acute bipolar depression and might be indicated for prophylactic long-term use in the majority of patients; the use of an antidepressant may be limited to treatment-resistant cases,[5–7] although this view has been questioned.[8]

Studies of the use of mood stabilizers in unipolar depression are even more limited, with the exception of lithium augmentation of standard antidepressant drugs. This treatment strategy was introduced by de Montigny et al.[9] in 1981, reproduced in several studies thereafter,[10] and is broadly used in clinical psychiatry. Open and controlled studies also suggest acute and prophylactic antidepressant efficacy of carbamazepine, which might be more pronounced in treatment-resistant and bipolar patients.[11] Augmentation strategies with carbamazepine showed results similar to those with lithium.[12] There are no placebo-controlled studies on the use of valproate in the treatment of acute depressive episodes. However, an open study

described a substantial response rate in unipolar patients.[13] In bipolar disorder, the antimanic properties of valproate are more pronounced than its antidepressive efficacy.[14,15]

Lamotrigine is a novel antiepileptic drug that is used in the treatment of partial and generalized seizures. In early clinical trials, a positive psychotropic effect of this compound was observed inducing improved mood, alertness, and social interaction in some patients.[16] A number of open-label trials and case reports describe beneficial effects of lamotrigine in different phases of bipolar disorder, including depressive episodes.[17–23] When given as monotherapy in depressed bipolar I outpatients, lamotrigine demonstrated a significant dose-dependent efficacy compared with placebo on several scales.[24] When used in rapid cycling, lamotrigine was superior to placebo in some, but not all, outcome criteria.[25] Interestingly, differences favoring lamotrigine were consistently larger for bipolar II than for bipolar I patients. Taken together, several lines of evidence indicate potent antidepressive properties of lamotrigine that might be superior to those of other mood stabilizers.

This study was designed to assess potential acute antidepressive effects of lamotrigine in a routine clinical patient population, to compare the combination of lamotrigine and paroxetine to paroxetine monotherapy with regard to efficacy and onset of action, and to detect putative drug interactions that would affect safety and tolerability of the lamotrigine–selective serotonin reuptake inhibitor (SSRI) combination.

METHOD

Patients

Patients eligible for this study were men and women from 18 to 65 years of age who were diagnosed by a clinical interview and a review of their history to suffer from an acute depressive episode requiring psychiatric intervention. This broad definition was used, and DSM-IV Axis II[26] diagnoses were not excluded to enable the participation of a routine clinical patient population. A diagnosis using DSM-IV criteria was established. Exclusion criteria consisted of serious medical conditions, suspected organic or drug-induced depressed states, epilepsy, pregnancy, or lactation. Effective contraception was required in female patients at risk of becoming pregnant. The use of fluoxetine, monoamine oxidase inhibitors, and depot neuroleptics was excluded within 8 weeks before study participation. Further exclusion criteria consisted of the use of oral anticoagulants and alcohol or drug abuse and a positive urine drug screen for illicit drugs. The patients were treated in the departments of psychiatry of the university hospitals of Freiburg and Munich, Germany.

Study Design and Procedures

This 2-center study employed a double-blind, fixed-dose, placebo-controlled, parallel-group design. Local ethics committee approvals were obtained, and patients gave written informed consent before study participation. Screening and baseline assessments consisting of medical and psychiatric history, physical and psychiatric examination, electroencephalogram, electrocardiogram, and laboratory testing confirmed that entry criteria were met. Equivalent numbers of patients were then randomly assigned to the 2 treatment arms. Study participants were randomly assigned to treatment groups in their sequence of randomization via a computer-generated blinded allocation list. The study blind was not broken until the final closing of the database.

All patients openly received paroxetine at 20 mg/day from days 1 through 14 and 40 mg/day from days 15 through 63 as a single dose in the morning. Patients in the lamotrigine group were additionally started on 25 mg/day of lamotrigine. The lamotrigine dose was escalated according to the following scheme to reach a target dose of 200 mg/day: days 1 through 14, 25 mg q.d.; days 15 through 28, 50 mg q.d.; days 29 through 35, 100 mg q.d., days 36 through 42, 150 mg q.d.; and days 43 through 63, 200 mg q.d. Active lamotrigine was dispensed as 25- and 100-mg film tablets. Trial participants in the placebo group received an equal number of placebo tablets identical in appearance to the active drug and followed the same escalation schedule. Compliance with the prescribed dosing regimen was determined by returned tablet counts at each treatment visit and retrospectively after unblinding by ascertaining that adequate plasma drug levels were maintained. Psychoactive drugs permitted as concomitant medication were lorazepam and oxazepam as needed for control of insomnia and agitation. Study physicians were urged to decrease the dose of these medications as early as possible.

Study visits were conducted at screening (within 7 to 2 days prior to treatment), at baseline (the day prior to the start of treatment), and on days 3, 7, 14, 21, 28, 35, 42, 49, and 63. At the screening visit, the patients underwent the following assessments: demographic characteristics, psychiatric history regarding affective disorders and other conditions, psychiatric and general drug history including history of skin rashes, current medical conditions, physical examination, vital signs including weight, electroencephalogram, electrocardiogram, urine drug screen for illicit and psychoactive drugs, urine pregnancy test for female patients with childbearing potential, clinical laboratory tests, the Hamilton Rating Scale for Depression[27] (HAM-D, 21 items), and the Clinical Global Impressions scale (CGI).[28] At the baseline visit, patients were randomly assigned to 1 of 2 treatment arms; at this and each treatment visit, the following assessments were performed: HAM-D; CGI for severity, improvement, therapeutic efficacy, and adverse events (from day 3 onward); adverse event assessment; vital signs; and record of study and concomitant medication. Blood samples for determination of plasma paroxetine and lamotrigine levels and

Table 1. Patient Characteristics[a]

Characteristic	Lamotrigine (N = 20)	Placebo (N = 20)
Sex, N (%)		
Male	6 (30)	7 (35)
Female	14 (70)	13 (65)
Age, y	39.6 ± 3.4	37.9 ± 1.9
Positive family history of depression, N (%)	6 (30)	11 (55)
Age at first episode, y	32.7 ± 3.3	28.7 ± 2.2
Lifetime number of depressive episodes	1.8 ± 2.7	2.27 ± 0.4
Lifetime number of suicide attempts	1.2 ± 0.2	1.3 ± 0.2
Lifetime number of hospitalizations	1.4 ± 0.4	1.7 ± 0.5
History of psychotic symptoms, N (%)	3 (15)	5 (25)
History of alcohol abuse, N (%)	2 (10)	1 (5)
History of eating disorder (anorexia), N (%)	2 (10)	1 (5)
Duration of last episode, mo	6.5 ± 2.9	4.1 ± 1.1
Duration of remission, mo	67.1 ± 20.3	41.8 ± 13.0
Duration of index episode, mo	4.0 ± 0.9	6.0 ± 1.5
HAM-D score at baseline	25.5 ± 1.8	25.0 ± 1.8
CGI-S score at baseline	5.2 ± 0.2	5.2 ± 0.2
Suicide attempt in index episode, N (%)	6 (30)	8 (40)

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression. All values shown as mean ± SEM unless otherwise noted. No differences between groups reached statistical significance.

Table 2. ICD-10 and DSM-IV Diagnoses

Diagnosis	ICD-10/ DSM-IV Codes	N
Lamotrigine group		
Recurrent depression, severe	F33.2/296.33	11
Recurrent depression, moderate	F33.1/296.32	5
Depressive episode, severe	F32.2/296.23	1
Bipolar I, depressive, severe	F31.4/296.53	2
Bipolar I, depressive, moderate	F31.3/296.52	1
Placebo group		
Recurrent depression, severe	F33.2/296.33	9
Recurrent depression, moderate	F33.1/296.32	3
Depressive episode, severe	F32.2/296.23	2
Bipolar I, depressive, severe	F31.2/296.53	1
Bipolar II, depressive, severe	F31.4/296.89	2
Bipolar II, depressive, moderate	F31.3/296.89	1
Dysthymia	F34.1/300.4	1
Depressed adjustment disorder	F43.21/309.0	1

for clinical laboratory testing were drawn at screening, baseline, and days 7, 14, 28, 35, and 63. At the last treatment visit (day 63 or premature discontinuation), the physical examination was repeated.

Data Analysis

The primary outcome measure for efficacy was the mean change from baseline in scores on the HAM-D during study therapy. Secondary measures were change from baseline in scores on subitems of the HAM-D and the CGI, differences in paroxetine levels between treatment groups, the use of concomitant medication, and survival in the study. Safety was assessed by summarizing treatment-emergent adverse events and determining changes from screen in clinical laboratory testing, vital signs, and weight values. Reasons for withdrawal from the study were listed, grouped, and compared between the groups.

The intent-to-treat population included all patients who were randomly assigned to study treatment. All tests were 2-tailed. p Values of less than .05 were regarded as significant. All values are given as mean ± SEM. The Student t test was used for continuous variables. The overall efficacy scales were tested for treatment group differences and effect of time and their interaction using a 2-way analysis of variance (ANOVA). Additionally, a responder analysis was performed on the last observed HAM-D and CGI scores comparing the rate of response among treatment groups by a Cochran-Mantel-Haenszel chi-square test. A further responder analysis compared the percentage of patients experiencing a 50% decrease from baseline in HAM-D total score. A survival analysis was performed using a log-rank test.

RESULTS

Sample Composition

Forty patients were randomly assigned to the 2 treatment groups; 20 received lamotrigine and 20 received placebo. All screened patients received study medication. 16 patients were prematurely withdrawn from the study (lamotrigine N = 7, placebo N = 9), the most common reasons being adverse events for lamotrigine and treatment failure for placebo.

Patient Characteristics

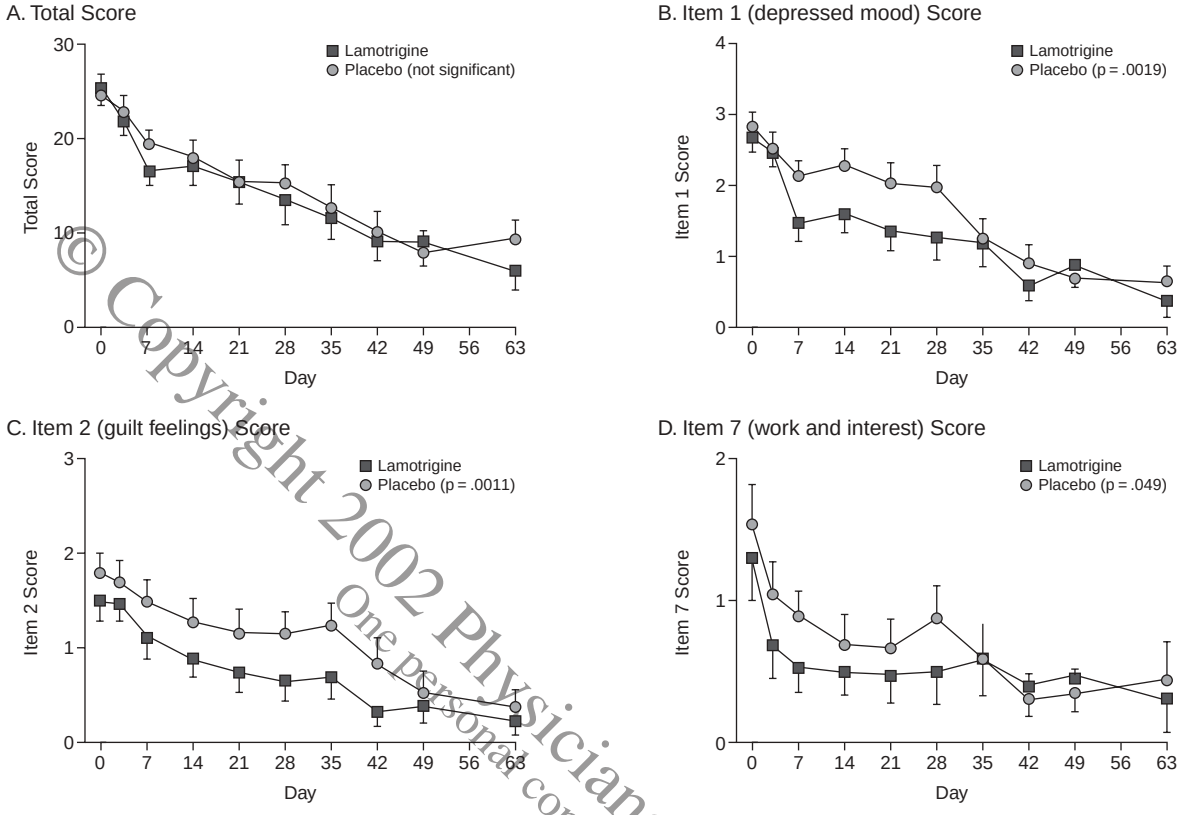
Demographic characteristics were comparable among the treatment groups (Table 1). Approximately 65% of the study participants were female, and the mean age of subjects was approximately 40 years with an age at first episode of around 30 years. A mean of 2 previous episodes, a high level of prior suicidality and hospitalization, and a HAM-D score of approximately 25 indicate a moderately to markedly ill patient population typical for the treatment setting at university hospitals. Furthermore, the mean duration of the index episode of 4 to 6 months and the prior treatment of most patients with 1 or more antidepressants indicate some degree of treatment resistance.

The most frequent diagnosis was a severe episode of a recurrent depressive disorder (lamotrigine N = 11, placebo N = 9). Three patients in the lamotrigine group and 4 in the placebo group were bipolar (Table 2).

Efficacy

HAM-D. The total HAM-D score declined over the duration of the trial in both groups, indicating a highly significant treatment effect ($p < .0001$). There was no significant difference between the groups. The HAM-D total

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores Observed at Each Study Visit for Patients Treated With Lamotrigine or Placebo[a]



[a]Values shown as mean (SEM).

score declined from 25.4 ± 1.8 at baseline to 6.1 ± 2.0 on day 63 in the lamotrigine group and from 25.0 ± 1.8 to 9.6 ± 1.8 in the placebo group (Figure 1A). When response was defined as a 50% decrease of the HAM-D total score at the beginning of the treatment phase, 11 patients responded in the lamotrigine group and 10 patients in the placebo group. In the responders, the 50% reduction of the HAM-D score was achieved on day 14.9 ± 3.1 for lamotrigine and on day 19.6 ± 5.1 for placebo, respectively. These data were not significantly different.

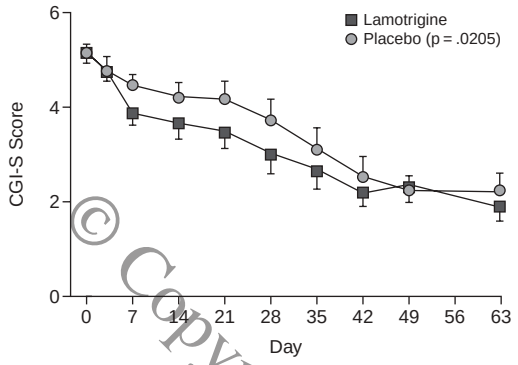
All 21 HAM-D items were analyzed separately. In most of the items, no significant treatment differences were observed. However, some core depressive symptoms improved significantly more in the lamotrigine group. When tested using ANOVA, mean scores for HAM-D items 1 (depressed mood; $p = .0019$), 2 (guilt feelings; $p = .0011$), and 7 (work and interest; $p = .049$) showed significant effects of the treatment group; item 3 (suicide; $p = .116$) approached significance. When the individual visits were compared for item 1, lamotrigine was superior to placebo from day 7 to day 28, reaching significance on days 7 ($p = .042$) and 14 ($p = .049$) and showing a strong trend on days 21 ($p = .099$) and 28 ($p = .103$). Similar results were found for items 2 and 7 (Figure 1B–1D).

To reveal a potential effect of subgroups, the HAM-D total scores were further analyzed. Neither bipolarity, duration of the index episode, prior treatment, nor gender significantly influenced treatment results. To test for a potential effect of severity, the patients were divided into 2 equal subgroups depending on their total HAM-D score. There was no difference in treatment effects between mildly or severely depressed patients.

CGI. The severity of depression measured by CGI-Severity of Illness scale (CGI-S) was influenced by lamotrigine. There was a significant difference between the treatment groups ($p = .0205$) and an overall effect of treatment ($p < .0001$; Figure 2). No significant differences were noted between the trial groups receiving lamotrigine and placebo regarding the ratings on the CGI for improvement, therapeutic efficacy, and adverse events. The severity of adverse events increased over the duration of the study in both groups.

Survival analysis. Thirteen of 20 patients in the lamotrigine group and 11 of 20 patients in the placebo group completed the study protocol until day 63. The patients' survival in the study was not significantly different between the treatment groups when tested using a log-rank test.

Figure 2. Clinical Global Impressions-Severity of Illness Scale (CGI-S) Ratings Observed at Each Study Visit for Patients Treated With Lamotrigine or Placebo[a]



[a]Values shown as mean (SEM).

Table 3. Treatment With Concomitant Medications

Concomitant Medication	Lamotrigine Group (N = 20) N[a]	Lamotrigine Group (N = 20) Duration[b]	Placebo Group (N = 20) N[a]	Placebo Group (N = 20) Duration[b]	p Value[c]
Lorazepam	11	25.92 ± 8.26	13	31.77 ± 6.69	0.58
Oxazepam	8	24.50 ± 4.98	12	34.25 ± 5.58	0.23
Internal medication	11	…	10	…	
Analgesics	6	…	9	…	
Antiemetics	1	…	1	…	

[a]Number of patients taking the indicated medication at any point during the trial.
[b]Any dose, mean ± SEM days of drug use.
[c]Duration, lamotrigine group vs. placebo group.

Concomitant medication. The amount of concomitant medication was used to provide additional measures of clinical stability and efficacy of the study medication. The majority of patients were treated for some time during the trial with benzodiazepines, mainly for sleeplessness. There was a trend toward fewer days on treatment with benzodiazepines in the lamotrigine group; however, this difference was not significant (Table 3).

Safety

Withdrawal from study. In the lamotrigine group, 3 patients were withdrawn for treatment failure or the occurrence of delusions (Table 4). In 3 patients, adverse events were the main reason for withdrawal from the study. One patient developed a benign skin rash on chest and upper extremities 5 days after the first intake of the study medication that resolved over some days after discontinuation of the study medication.

Two patients developed a decrease in white blood cells (WBCs). A 21-year-old woman was noted for a decrease of WBC count starting 15 days after inclusion in the study. After 5 weeks, when she was already discharged from hospital, her WBC count was 2500/µL with 28.0% of neutrophils. The study medication was stopped and she was rehospitalized. This was reported as a serious adverse event for a putative high risk for infection. The study blind was not broken. Paroxetine was continued. The WBC count slowly recovered, although 6 weeks later, it was still only 3100/µL with 47.5% of neutrophils. It was revealed retrospectively that some weeks before her inclusion in the study, her WBC count had been 2800/µL; however, the WBC count had been within normal limits at baseline. The patient had a history of anorexia. This adverse event might possibly not have been related to lamotrigine; however, this cannot be completely excluded.

In a 36-year-old man, the WBC count was 8900/µL at inclusion in the study. On day 14, it dropped to 4200/µL and on day 28, to 3500/µL. The study was stopped on day 48 because of a WBC count of 2900/µL with 53.2% of neutrophils. Three weeks later, the WBC count was within the normal limits again under medication with venlafaxine.

Table 4. Reasons for Withdrawal From Study[a]

Day[b]	Reason for Withdrawal
Lamotrigine Group	
15	AE: rash
20	Treatment failure
23	Consent withdrawn
31	Treatment failure
36	SAE: neutropenia
48	AE: leukopenia
53	AE: delusion (hypochondriac concern)
Placebo group	
11	Treatment failure
14	AE: delusion, treatment failure
21	Protocol violation
26	AE: delusion, treatment failure
28	AE: delusion
32	Treatment failure
36	Treatment failure
54	Treatment failure
57	Treatment failure

[a]Abbreviations: AE = adverse event, SAE = serious adverse event (requiring rehospitalization).
[b]Days on treatment with study medication before withdrawal from the trial.

In the placebo group, treatment failure was the main reason for discontinuation of the study (Table 4). In addition, 3 patients developed delusions requiring antipsychotic intervention. No switch to mania or suicide attempt was reported in either group.

Adverse events. The study medication was generally well tolerated. Most patients did not experience major adverse events. The most commonly reported adverse event was headache, which was observed more frequently in the placebo group and seems not to be related to the study medication. Three patients in the lamotrigine group and 1 patient in the placebo group reported a rash that led to withdrawal of 1 patient on lamotrigine treatment as noted above. There were no significant differences between the treatment groups regarding the occurrence of adverse

Table 5. Adverse Events[a]

Adverse Event	Lamotrigine (N = 20)	Placebo (N = 20)
Diaphoresis	5	6
Upper respiratory tract infection	5	6
Nausea/emesis	4	3
Vertigo	4	1
Headache	4	8
Tremor	4	3
Blurred vision	3	2
Rash	3	1
Sedation	2	4
Dry mouth	2	1
Leukopenia/neutropenia	2	1
Delusions	1	3
Constipation	1	4
Body pain	1	2
Urinary tract infection	1	2
Pruritus	1	2

[a]Values shown as number of patients reporting the indicated adverse event. All adverse events are listed that were reported more than once in any treatment group.

events (Table 5). There were no apparent treatment group differences in laboratory results, vital signs, or weight. The mean body weight on day 63 was 100.1% ± 5.0% of the baseline weight for lamotrigine and 96.7% ± 5.5% for placebo, respectively. As there were 2 cases of neutropenia in the lamotrigine group, we further examined the course of the WBC count over the duration of the study. Neither time nor treatment group significantly influenced the WBC count.

Plasma drug levels. The plasma paroxetine levels did not differ significantly between the groups. There seems to be no pharmacokinetic interaction between lamotrigine and paroxetine. In the lamotrigine group, the paroxetine level was 32.09 ± 6.16 mg/L on day 7 and increased to 111.02 ± 25.18 mg/L on day 63. In the placebo group, paroxetine increased from 22.2 ± 5.58 mg/L to 144.56 ± 38.83 mg/L. The lamotrigine level ranged between 0.57 ± 0.13 mg/L on day 7 and 3.16 ± 0.48 mg/L on day 64, which is on the lower side of the therapeutic window for epilepsy (2–10 mg/L).

DISCUSSION

This is the first double-blind, placebo-controlled trial evaluating the antidepressive properties of lamotrigine in a routine patient population consisting mostly of unipolar depressed subjects. The study results partially support the previously shown antidepressive properties of lamotrigine and may extend its spectrum of efficacy into the field of unipolar depression.

The concurrent application of lamotrigine and paroxetine did not result in a significant difference of the HAM-D total score, the primary outcome measure of this trial, compared with paroxetine alone. However, when given in addition to paroxetine, lamotrigine was superior to placebo in improving core symptoms of depression such as depressed mood, guilt feelings, work nonproductivity, and lack of interest. On the other hand, there was no detectable effect of lamotrigine on somatic symptoms, sleep, and anxiety. Lamotrigine by itself is not sedating; this is supported by the fact that only 2 of 20 patients on lamotrigine treatment complained of sedation. This lack of sedation might partly explain the failure of lamotrigine to produce a significant difference in the 21-item HAM-D total score when compared with placebo. The HAM-D is weighted toward somatic symptomatology relative to other scales such as the Montgomery-Asberg Depression Rating Scale,[29] which might have been more suitable to separate efficacy differences between placebo and lamotrigine. However, significant differences in secondary outcome parameters such as CGI-S ratings, fewer days on treatment with benzodiazepines, and fewer withdrawals for treatment failure in the lamotrigine group provide evidence for the antidepressive properties of this drug. These findings are compatible with those of Calabrese et al.[24] in their double-blind trial. They showed that lamotrigine, 50 and 200 mg/day, is superior to placebo when used as monotherapy in bipolar I depressed outpatients. Better separation between placebo and lamotrigine on item 1 as compared with the total HAM-D score was also reported.

One of the principal findings of this study is that lamotrigine may accelerate the onset of action of the antidepressant. Significant differences between the lamotrigine and the placebo group could be noted as early as day 7 of treatment in some items. Most items failed to separate between lamotrigine and placebo from week 4 onward; this finding might be explained by the expected onset of action of the potent antidepressant paroxetine. Most patients in both groups finally remitted from their depression at the end of the trial to an extent that may be wholly attributable to the antidepressive efficacy of paroxetine; however, patients on lamotrigine treatment improved significantly faster. This is even more surprising because dose and plasma levels of lamotrigine were far from achieving therapeutic levels as used in epileptology in the first weeks of the trial due to the slow dose-escalation scheme. Lamotrigine was used in this study as an acceleration strategy for the antidepressant paroxetine. Our results are comparable to previous reports on thyroid hormone acceleration strategies.[30]

Lamotrigine acts in an additive manner to an SSRI. Therefore, it might be expected that the mode of action of lamotrigine in depression is different from that of an SSRI. Moreover, results from auditory evoked potential paradigms used as a tool to indicate central serotonergic neurotransmission[31] suggest a nonserotonergic mode of action. The results of these measurements will be reported in a future publication.

Lamotrigine was generally well tolerated by most patients in this study. However, some patients reported

serious adverse events. The occurrence of adverse events was the main reason for withdrawal from the study in the lamotrigine group as opposed to treatment failure in the placebo group. Two patients on lamotrigine treatment experienced leukopenia and were subsequently withdrawn from the trial. In one of these patients, the clearly reduced WBC count might have been due to a preexisting medical condition or anorexia; in the other patient, a more mildly reduced WBC count might have been related to the study medication. Leukopenia is a little-known complication of lamotrigine therapy; however, there are several reports on it.[32–35] The incidence of rash (3 of 20 in the lamotrigine group, 1 of 20 on placebo treatment) was similar to that observed with lamotrigine treatment in open and placebo-controlled epilepsy clinical trials.[36] There was no evidence for any drug interaction between lamotrigine and paroxetine. There was no difference in the plasma paroxetine levels between the lamotrigine and placebo groups. Lamotrigine levels were not excessively high, which does not support an effect of a putative inhibition of hepatic cytochrome P450 enzymes by paroxetine on lamotrigine metabolism.[37] Given the low plasma levels of lamotrigine in this dose range and the lack of pharmacokinetic drug interaction, a routine control of plasma levels seems not to be indicated in clinical practice.

This study had limitations that could confound the interpretation of the data, the most important being the small number of patients included in this trial together with a high dropout rate. The inclusion of unipolar and bipolar depressed patients might have been problematic in light of the ongoing discussion on separate etiologies and distinct clinical features of these two affective disorders. However, the few bipolar patients in our study did not differ from the unipolar population with respect to treatment outcome, and there was no switch to mania. Furthermore, the goal of this study was to examine a routine clinical patient population including a limited percentage of depressed bipolar patients. The use of an antidepressant as monotherapy in one arm of the study protocol is compatible with generally accepted European treatment habits.[8] The power of the study was limited by the use of lamotrigine as adjunct medication to an antidepressant. A controlled monotherapy trial with unipolar patients was not feasible due to ethical considerations; in contrast, the absence of broadly accepted pharmacologic treatment guidelines has justified monotherapy trials in bipolar depression.[24] The concurrent application of lamotrigine and paroxetine might have prevented the trial from demonstrating significant changes in its primary outcome measure. Further studies are warranted to examine a putative usefulness of lamotrigine when added sequentially to an antidepressant, e.g., in therapy-refractory patients. It would have been desirable to obtain higher doses and plasma levels of lamotrigine in order not to preclude maximum benefits and separation from placebo; however, this was prevented by an increased risk for skin reactions with faster dose-escalation schemes.

In addition to the recently reported promising results in bipolar II depressed patients, our study suggests antidepressive properties of lamotrigine in unipolar patients. Low-dose lamotrigine may accelerate the onset of other antidepressants. Monotherapy studies should examine if the antidepressant efficacy of lamotrigine could be compared to that of typical antidepressants. Furthermore, the substance might be suitable to be used in augmentation strategies for therapy-refractory depressive episodes and should be compared with lithium. To date, lamotrigine seems to be the only putative mood stabilizer with potent antidepressive properties.

Drug names: carbamazepine (Tegretol and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), lorazepam (Ativan and others), oxazepam (Serax and others), paroxetine (Paxil), venlafaxine (Effexor).

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