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Letter to the editors

The effect of lamotrigine on platelet serotonin concentration in patients with bipolar depression

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Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an antiepileptic drug effective in the treatment of bipolar disorder in a depressive phase (Calabrese et al. 1999; Goldsmith et al. 2003) and in prevention of relapse of bipolar depression (Calabrese et al, 2003). Preclinical studies suggested that antidepressant effects of lamotrigine might be related to alterations of serotonin (5-hydroxytryptamine, 5-HT) neurotransmission (Consoni et al. 2006; Ahmad et al. 2005). Blood platelets might be used as a peripheral model for some processes (5-HT uptake, 5-HT₂ receptors binding and monoamine oxidase activity) in the central 5-HT synaptosomes (Camacho and Dimsdale 2000). Since there are no data evaluating the effects of lamotrigine on platelet markers in patients, the aim of the study was to determine the effects of 6-weeks lamotrigine treatment on platelet 5-HT concentration in patients with bipolar I disorder currently depressed (bipolar depression), and to compare the effect of lamotrigine with the effect of 6-weeks paroxetine treatment on platelet 5-HT concentration in patients with major depressive disorder (MDD).

Both patients with bipolar depression and MDD were diagnosed by a structured clinical interview (First et al. 1995) for DSM-IV disorders (APA, 1994). In a nonrandomized prospective, open-label, comparative, 6-weeks study, 28 female patients 48.8 (SD 11.5) years old with bipolar depression were treated with lamotrigine (25-100 mg/day), and 51 female patients with MDD 49.5 (SD 7.9) years old received paroxetine (20 mg/day). Lamotrigine was added to the current treatment in 14 patients: lithium (6 patients, 600-900 mg/day; lithium plasma concentration 0.55-0.80 mmol/l); quetiapine (2 patients, 300-400 mg/day), risperidone (3 patients, 2 mg/day), olanzapine (3 patients, 5-10 mg/day). All patients were allowed to take diazepam (up to 15 mg/day). Participants have signed informed consent, approved by the local Ethics Committee. They had ≥ 18 scores on the 17- items Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960). Patients with bipolar depression additionally required less than 7 scores on Young Mania Rating Scale (Young 1978). The exclusion criteria were (a) substance abuse disorder within the

previous 6 months; (b) diagnosis of schizophrenia, schizoaffective disorder, dementia, posttraumatic stress disorder; (c) presence of psychotic features; (d) treatment with any medication known to influence platelet 5-HT concentration in previous 2-4 weeks; (f) duration of current depressive episode for more than 2 years, to exclude chronic depression; (g) for patients with BD a history of previous non-response to lamotrigine or lamotrigine-induced rash. Depressive symptoms (evaluated using HAMD) and platelet 5-HT concentration (nmol/mg proteins), measured using spectrofluorimetric method (Muck-Seler et al. 2002), were determined at baseline (a day before lamotrigine or paroxetine administration), and after 6 weeks of treatment. No symptoms of mania have emerged during lamotrigine treatment. Drop outs: 2 patients in lamotrigine group: one patient was lost during follow-up, and the other patient was excluded because of the rash, which was not visible on the examination, but the patient claimed she had a rash a day before; and 3 patients in paroxetine were excluded since they complained of worsening of their depressive symptoms. No serious adverse events occurred during the study. Statistical evaluation of the results, expressed as means \pm standard deviations (SD), was performed using repeated measures analysis of variance (RMANOVA) followed by Tukey's test and multifactorial analysis of variance (MANOVA) with significance accepted when $P < 0.05$.

Patients with bipolar depression or MDD had significantly ($P < 0.001$, RMANOVA) lower platelet 5-HT concentration after 6 weeks of lamotrigine or paroxetine treatment than at baseline (Table 1). MANOVA ($df=3,141$) revealed the significant main effects ($F=46.01$, $P < 0.001$), significant effect of time (baseline vs. 6 weeks) of treatment ($F=116.11$, $P < 0.001$), significant effects of drugs (lamotrigine vs. paroxetine; $F=16.15$, $P < 0.001$) and significant interaction between time and drugs ($F=5.48$, $P=0.021$) on platelet 5-HT concentration. To further assess the inhibitory effect of lamotrigine on platelet 5-HT concentration in patients with bipolar depression, and to evaluate the possible effects of lamotrigine added to the current treatment with antipsychotic drugs or lithium on platelet 5-HT concentration, patients with bipolar depression were subdivided into those treated with lamotrigine (only) and lamotrigine with antipsychotics, or lamotrigine without lithium, and lamotrigine with lithium. The results showed (Table 1) the significant (RMANOVA) decrease in platelet 5-HT values in both patients with bipolar depression taking lamotrigine only and in those taking lamotrigine with antipsychotic drugs or lithium. At baseline patients with bipolar depression (24.54 ± 2.67) and MDD (26.52 ± 2.45) had similar total HAMD scores. The significant (RMANOVA) decreases in total HAMD scores were observed after treatment with lamotrigine (9.77 ± 7.54) in bipolar [$F(1,25)=165.517$, $P < 0.001$], or paroxetine (11.98 ± 8.62) in MDD [$F(1,47)=165.879$, $P < 0.001$] patients.

To the best of our knowledge, this is the first report showing significantly lower platelet 5-HT concentration in bipolar depressed patients treated for 6 weeks with lamotrigine in relatively low doses (up to 100 mg/day). Lower platelet 5-HT concentration might be associated with suicidal behaviour, previous treatment with selective serotonin reuptake inhibitors (SSRI), or female gender (see Muck-Seler et al., 1996; 2005). Since we included only female, non-suicidal patients matched for age, who were not previously treated with SSRI, platelet 5-HT concentration was not significantly affected by these variables. This inhibitory effect of lamotrigine on platelet 5-HT concentration persisted

when lamotrigine was added to the current antipsychotic or lithium treatment. Our results agree with *in vitro* data showing that lamotrigine inhibited 5-HT uptake in rat brain synaptosomes (Southam et al., 1998), and with the data from experimental animals, where lamotrigine reversed the chloroamphetamine-induced 5-HT syndrome in rats (Southam et al.1998), and reduced the immobility in an animal model of depression, suggesting that antidepressant effect of lamotrigine is mediated also by 5-HT mechanisms (Consoni et al. 2006). The antidepressant effect of lamotrigine in patients with bipolar depression was similar to the effect of paroxetine on platelet 5-HT concentration and on the HAMD scores in patients with MDD (Muck-Seler et al. 2002; 2005), probably due to its inhibitory effect on 5-HT uptake in human platelets *in vitro* (Southam et al. 1998). The antidepressant effect of lamotrigine (present study) is in line with data showing that lamotrigine, as an augmentation therapy in depression, accelerated the onset of action of paroxetine (Normann et al. 2002) and fluoxetine (Barbosa et al. 2003). In conclusion, lamotrigine, similarly to paroxetine in patients with MDD, decreased platelet 5-HT concentration in patients with bipolar depression. Our results suggest that lamotrigine possesses *in vivo* 5-HT uptake inhibiting property, and this effect might have contributed to its antidepressant activity.

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Table 1. Platelet 5-HT concentration (mean \pm SD) in female patients with bipolar depression (BD), before and after 6 weeks of lamotrigine treatment, in female patients with major depression (MDD), before or after 6 weeks of paroxetine treatment, and in patients with BD subdivided into groups with or without lithium or antipsychotic treatment. N is the number of subjects.

Treatment	N	Platelet 5-HT concentration (nmol/mg proteins)	Statistical analysis RMANOVA		
			<i>F</i>	<i>df</i>	<i>P</i>
<i>Patients with BD</i>					
before lamotrigine	26	1.44 \pm 0.45			
after lamotrigine	26	0.93 \pm 0.34 ^d	21.74	1,25	0.001
<i>Patients with MDD:</i>					
before paroxetine	48	1.30 \pm 0.49			
after paroxetine	48	0.46 \pm 0.34 ^e	141.35	1,47	0.001
<i>Patients with BD</i>					
Lamotrigine only					
before treatment	12	1.59 \pm 0.47			
after treatment	12	1.03 \pm 0.46 ^a	9.34	1,11	0.011
Lamotrigine + antipsychotics					
before treatment	14	1.31 \pm 0.40			
after treatment	14	0.84 \pm 0.16 ^c	12.16	1,13	0.004
Lamotrigine without lithium					
before treatment	20	1.47 \pm 0.41			
after treatment	20	0.95 \pm 0.37 ^f	22.33	1,19	0.001
Lamotrigine with lithium					
before treatment	6	1.49 \pm 0.40			
after treatment	6	0.72 \pm 0.07 ^b	18.59	1,5	0.008

^a*P*=0.011, ^b*P*=0.008, ^c*P*=0.004, ^{d,e,f} *P*<0.001 vs. corresponding values before treatment (Tukey's test)