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Lamotrigine treatment of aggression in female borderline patients, Part II: an 18-month follow-up

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Abstract

Borderline patients often display pathological aggression. We previously tested lamotrigine, an anti-convulsant, in therapy for aggression in women with borderline personality disorder (BPD) (J Psychopharmacol 2005; 19: 287–291), and found significant changes on most scales of the State-Trait Anger Expression Inventory (STAXI) after eight weeks. To assess the longer-term efficacy of lamotrigine in therapy for aggression in women with BPD, this 18-month follow-up observation was carried out, in which patients (treated with lamotrigine: $n = 18$; former placebo group: $n = 9$) were tested every six months. According to the intent-to-treat principle, significant changes on all scales of the STAXI were observed in the lamotrigine-treated subjects. All subjects tolerated lamotrigine relatively well. Lamotrigine appears to be an effective and relatively safe agent in the longer-term treatment of aggression in women with BPD.

Keywords

borderline personality disorder, aggression, lamotrigine

Introduction

The treatment of symptoms in borderline personality disorder (BPD), including aggression, has been studied intensively (Zanarini, 2004). The efficacy of selective serotonin reuptake inhibitors, atypical neuroleptics and with the exception of valproate and carbamazepine, anti-epileptic drugs in the treatment of pathological aggression remains to be established (Fava, 1997; Azouvi *et al.*, 1999; Tariot *et al.*, 1998; Nickel *et al.*, 2004; Nickel *et al.*, 2005; Loew *et al.*, 2006; Nickel *et al.*, 2006). Effective pharmacological interventions with lamotrigine, an anti-convulsant, in borderline patients have also been reported (Pinto and Akiskal, 1998; Preston *et al.*, 2004); however, until now, only one controlled trial is known, which employed this medication for patients with BPD (Tritt *et al.*, 2005). That study was carried out in a double-blind and placebo-controlled design with women with BPD (Tritt *et al.*, 2005), and after eight weeks' treatment with a daily dose of up to 200 mg lamotrigine, significant changes on most scales of the State-Trait Anger Expression Inventory (STAXI) (Schwenkmezger *et al.*, 1992) were observed. In the present, follow-up observation of patients who participated in the above-mentioned study (Tritt *et al.*, 2005), the longer-term influence of lamotrigine on anger symptoms in women with BPD was investigated.

Methods

The procedure for recruitment of the study sample has already been described in detail in our first report (Tritt *et al.*, 2005).

The exclusion criteria for the follow-up observation were schizophrenia, current use of psychotropic medication in the previous placebo group (PG), termination of lamotrigine in the lamotrigine group (LG), as well as current psychotherapy, current suicidal ideation, severe somatic illness or abuse of drugs or alcohol in either group. Potential subjects were also excluded if they were pregnant, planning to be, or not using contraception. During the course of the follow-up study, additional subjects were excluded who missed more than one evaluation.

The subjects were invited to participate in face-to-face interviews. The possible side effects were fully explained once again. Primary

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outcome measures were changes in the STAXI (Schwenkmezger *et al.*, 1992), described in detail elsewhere (Tritt *et al.*, 2005).

The necessary sample size calculation and the randomization were described in detail, in our report of the the first study, in which female patients were treated for eight weeks in 2004 with a daily dose of up to 200 mg lamotrigine (LG: $n = 18$) or with a placebo (PG: $n = 9$), and tested with STAXI every week (Tritt *et al.*, 2005). Following the final testing, the blind was broken.

After completion of the above-mentioned study, an 18-month follow-up was carried out, in which the patients (LG: $n = 18$; former [Ex-PG]: $n = 9$) were tested every six months. The patients in the LG took continued taking 200 mg lamotrigine daily. The Ex-PG took neither lamotrigine nor placebo. During the course of the trial, the intermediate results were not analysed. After eighteen months, both groups were tested for the last time and physically examined. Ten subjects dropped out; of these, two were from the PG and one from the LG during the placebo-controlled study (Tritt *et al.*, 2005), and seven dropped out during the follow-up: two who missed more than one evaluation (one from the LG), one from the LG who changed residence, one from the LG due to termination of lamotrigine, and three from the Ex-PG due to initiation of therapy with lamotrigine or another psychopharmica. The test-questionnaires were filled out by the patients both independently and anonymously. Our staff checked the data for completeness. The study was concluded according to plan.

Data analysis

We used the statistical program SPSS, Version 12 (SPSS Inc. Chicago, Illinois, USA) to analyse the data according to the intend-to-treat principle. Data are presented as means and standard deviations.

A two-factor repeated measure analysis of variance was performed. The treatment condition was defined as the between-subject factor, and the measurements in time as the within-subject factor. When the assumptions for performing the repeated measure analysis were not given, the results were adjusted using the Greenhouse-Geisser Epsilon (Stevens, 1992). To assess whether there were differences at the initial and final points, multiple comparisons were performed using contrasts for each treatment condition. The significance levels were corrected using the Bonferroni correction. Changes in the dichotomy parameters, employment and partnership were analysed by means of the binominal test (Dufner *et al.*, 1992).

Source of funding and ethical considerations

The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions and its design approved by the clinic's 'Ethikkomission' (the German equivalent of the Committee on Human Subjects). All subjects gave written informed consent. The study was conducted independent of any institutional influence and was not funded. There were no conflicts of interest.

Results

The detailed medical and social data from the patients of both groups were described and compared with each other in the previous publication (Tritt *et al.*, 2005).

Table 1 summarizes the changes in both groups over the course of the entire study. The LG experienced a significantly greater changes than the placebo/Ex-PG on all STAXI scales.

No serious side effects were observed. In isolated cases, relatively mild rash, dizziness, headache and nausea were reported. Two subjects from the Ex-PG and one from the LG engaged in self-mutilation, and one from the Ex-PG attempted suicide during the study. In addition, weight loss was observed after eighteen months treatment. In the LG, weight loss was no more significant than in the (PG) [LG: starting weight MV = 78.6 ± 10.1 kg, weight after 18 months MV = 77.8 ± 11.9 kg; Ex-PG: starting weight MV = 77.3 ± 11.4 kg, BMI = 26.8, weight after 18 months MV = 78.5 ± 13.7 kg; p(IE) = 0.65, p(FE) = 0.01, P (group × time effect) = 0.43, P (group effect) = 0.31].

Discussion

During the entire observation period, there was a significantly greater change on all STAXI scales (Schwenkmezger *et al.*, 1992) in the lamotrigine-treated group that in the placebo/ex-PG. Specifically, lamotrigine was more effective in treating the aggression component of borderline psychopathology, which corroborates the previous report (Tritt *et al.*, 2005). Among our patients, lamotrigine appeared to influence the intensity of the perceived feeling of anger as well as the threshold for perceiving it. The way aggression was processed intra-psychologically was possibly also influenced, and in the final analysis even the socially desirable control of anger as well.

The most common side effects of lamotrigine are headache, nausea, dizziness, infection, dry mouth, diarrhea, somnolence, ataxia, tremor, insomnia, rash and withdrawal (Messenheimer *et al.*, 1998). All our patients tolerated it well or very well; unpleasant symptoms were reported only in isolated cases. Moderate weight loss was observed and was usually regarded as beneficial. In the literature, both moderate weight loss and mood stabilization have been attributed to lamotrigine (Calabrese, 2003). However, our study could only demonstrate that weight remained constant with lamotrigine.

The results of this trial are consistent with those of earlier studies which found that anti-convulsant medications are effective in the treatment of pathologic aggression (Fava, 1997; Azouvi *et al.*, 1999; Tariot *et al.*, 1998). Rizvi (2002) and Pinto and Akiskal (1998) reported decreased symptoms of aggression in borderline patients undergoing lamotrigine therapy.

One of the limitations was that the sample size was relatively small, and both the blind and placebo medication were discontinued. In addition, the relatively high dropout rate limits the extent to which the results can be generalized. The study focused on only one dimension of BPD in borderline women, namely, aggressive-impulsivity. The effects of lamotrigine on other dimensions of

Table 1 Changes in all scales of the STAXI

	State-anger (S-A)[a]		Trait-anger (T-A)[a]		Anger-in (AI)[a]		Anger-out (AO)[a]		Anger-control (AC)[a]	
	LG	Ex-PG	LG	Ex-PG	LG	Ex-PG	LG	Ex-PG	LG	Ex-PG
IE (LG: $n = 18$; PG: $n = 9$)	32.2 ± 3.5	31.7 ± 3.9	30.7 ± 3.7	29.4 ± 3.2	22.3 ± 3.5	23.2 ± 3.3	25.3 ± 3.5	24.8 ± 3.1	17.2 ± 2.9	17.9 ± 2.5
FE (LG: $n = 17$; PG: $n = 7$)	21.1 ± 2.9	29.6 ± 3.2	22.1 ± 3.2	27.9 ± 3.6	20.8 ± 4.5	23.8 ± 4.9	17.8 ± 3.0	23.2 ± 3.7	20.2 ± 2.2	17.6 ± 2.9
6M (LG: $n = 16$; PG: $n = 7$)	21.2 ± 3.6	30.1 ± 2.8	22.2 ± 3.2	28 ± 2.1	20.7 ± 4.9	24.9 ± 4.3	19.1 ± 4.2	24.5 ± 5.2	22.1 ± 2.7	17.6 ± 2.5
12M (LG: $n = 14$; PG: $n = 5$)	19.9 ± 3.2	31.4 ± 1.4	19.8 ± 1.8	29.6 ± 1.8	18.7 ± 2.6	27.1 ± 4.9	17.2 ± 1.9	23.7 ± 4.6	22.4 ± 2.0	16.3 ± 2.8
18M (LG: $n = 14$; PG: $n = 3$)	16.8 ± 4	31.6 ± 1.4	17.9 ± 2.1	30 ± 1.8	17.9 ± 2.5	27.7 ± 5.1	16.3 ± 2.1	25.2 ± 4.6	23.2 ± 2.0	16.0 ± 2.8
P (IE)	$P = 0.72$	$P = 0.35$	$P = 0.52$	$P = 0.70$	$P = 0.52$					
P (FE)	$P < 0.01$	$P < 0.01$	$P = 0.12$	$P < 0.01$	$P = 0.01$					
P (group × time effect)	$P < 0.01$	$P < 0.01$	$P = 0.02$	$P < 0.01$	$P < 0.01$					
P (group effect)	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$					

[a]mean ± standard deviation. Abbreviations: LG, lamotrigine treated group; Ex-PG, previous placebo group; IE, initial evaluation; FE, final evaluation from the first study (Tritt *et al.*, 2005), 6, 12, 18 – no. of months following discontinuance of the blind when examination took place (current study), P(IE) = significance level for the comparison LG versus PG at the time point IE, P(FE) = significance level for comparison LG versus PG at time point FE, P (group × time effect) indicates whether the two groups have changed differently over time, (this is the important test for significance of treatment effects in the repeated measure design), P (group effect) indicates a systematic difference between the groups.

BPD, such affective dysregulation, cognitive perceptual impairment and disturbed relationships, were not evaluated. Additional placebo-controlled trials of longer duration are needed to see if these results can be replicated.

Following a longer period of observation, lamotrigine appears to be a safe and effective agent for improving aggression in borderline women (Tritt *et al.*, 2005), and the treatment effect ascertained in a placebo-controlled study (Tritt *et al.*, 2005) could be corroborated in this subsequent observational study. The results of this trial corroborates other reports in which anti-convulsants (Tariot *et al.*, 1998, Nickel *et al.*, 2004; Nickel *et al.*, 2005; Tritt *et al.*, 2005) were found to be effective in the treatment of pathologic aggression.

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