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# Self-reported aggressiveness during treatment with levetiracetam correlates with depression

Marco Mula [a,b,*], Niruj Agrawal [a,b,c], Zainab Mustafa [c], Krithika Mohanalingham [c], Hannah R. Cock [a,b], Dora A. Lozsadi [a,b], Tim J. von Oertzen [d]

[a] Epilepsy Group, Atkinson Morley Regional Neuroscience Centre, St George's Hospital, London, UK
[b] Institute of Medical and Biomedical Sciences, St George's University of London, UK
[c] Department of Neuropsychiatry, South West London & St George's Mental Health Trust, London, UK
[d] Department of Neurology, Wagner-Jauregg Neuroscience Centre, Kepler Universitätsklinik, Linz, Austria

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ABSTRACT

*Purpose:* The purpose of this study was to identify clinical correlates of self-reported aggressiveness (SRA) in patients with epilepsy treated with levetiracetam (LEV) with special reference to the role of depression.
*Methods:* A consecutive sample of adult outpatients with epilepsy was assessed with the Neurological Disorder Depression Inventory for Epilepsy, the Adverse Event Profile (AEP), and the Emotional Thermometer.
*Results:* From a total sample of 163 consecutive patients treated with LEV, SRA at any level (from rarely a problem to always) was associated with a 7-fold increased risk of being depressed (95% CI: 3.0–17.5; $p < 0.001$). Self-reported aggressiveness was reported as "always" a problem by 9.8% of the patients. In these patients, apart from depression, SRA was associated with high AEP total scores (55.1 vs. 39.3; $p < 0.001$) and polytherapy (43.8% vs. 19.8%; $p = 0.034$). Anxiety scores were not elevated (4.9 vs. 3.6; $p = 0.183$).
*Conclusions:* Self-reported aggressiveness during treatment with LEV is not an isolated symptom but is associated with depressed mood. Anxiety-mediated mechanisms do not seem to be involved.



## 1. Introduction

Aggressiveness is quite a neglected area in psychopharmacology and even more in epileptology. Aggressive behavior as an ictal phenomenon is very rare, while it may be seen in the context of postictal confusion [1]. Interictal aggression is also rare but can occasionally be seen in patients with temporal lobe epilepsy, and it is usually described as episodic dyscontrol or, more precisely, as intermittent explosive disorder [2]. From a psychopharmacological point of view, many studies addressed the treatment of aggressiveness [3,4], but data on drug-induced deterioration of aggressiveness or drug-induced aggressive behavior are more than scant.

Levetiracetam (LEV) is a second generation antiepileptic drug (AED) that, over the past 10 years, has been widely used not only among epileptologists but also by general neurologists, emergency physicians, neurointensivists, and neurosurgeons [5] because it showed to be not only effective but also easy to use (i.e., linear pharmacokinetics, lack of drug–drug interactions) and well tolerated [6]. However, since the very beginning, mood and behavioral problems were reported as treatment-emergent adverse events, namely agitation, anxiety, depression, emotional lability, hostility, nervousness, and, rarely, psychosis [7,8]. Self-reported aggressiveness seems to be a problem more often in patients taking LEV than in those taking other AEDs [9]. It is still controversial whether a fast titration schedule of the drug is a risk factor [7,8]. However, it seems that some patients are generally predisposed to develop this psychiatric reaction. Some authors emphasized the previous psychiatric history [7], while others identified a specific genetic variation in dopaminergic activity [10].

The mechanism of action of LEV differs from that of currently available AEDs and appears to be mediated by the synaptic vesicle protein SV2A, resulting in an inhibition of neurotransmitter release from the end terminals [11]. However, LEV has been shown to potentiate GABAergic neurotransmission [12] and to modulate high voltage N-type voltage dependent calcium channels [13].

The aim of this study was to identify clinical correlates of self-reported aggressiveness in patients with epilepsy treated with LEV with special reference to the role of depression.

* Corresponding author at: Epilepsy Group, Atkinson Morley Regional Neuroscience Centre, St George's Hospital, Blackshaw Road, London SW17 0QT, UK. Tel.: +44 2087254107; fax: +44 2087254591.
*E-mail address:* mmula@sgul.ac.uk (M. Mula).

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## 2. Methods

Data from a consecutive sample of patients with an established diagnosis of epilepsy attending the Epilepsy Clinics of the Atkinson Morley Outpatient Department, St George's Hospital in London were analyzed. As part of our routine assessment, all patients receive, at each visit, the Neurological Disorder Depression Inventory for Epilepsy (NDDIE) [14], the Adverse Event Profile (AEP) [15], and the Emotional Thermometer (ET) [16]. As per Research Ethic Committee (REC) advice, research limited to secondary use of anonymized information previously collected in the course of normal care is excluded from formal REC review.

The NDDIE is a well-known clinical instrument, developed for the rapid and objective detection of a major depressive episode in patients with epilepsy. It has been found to be a very practical and user-friendly screening instrument in an outpatient setting.

The AEP is a 19-item, self-reported instrument specifically developed to investigate side effects of AEDs in patients with epilepsy. It is possible to analyze the score of individual symptoms as well as calculate an overall symptom score. Each symptom is quantified on a four-point Likert scale, with 1 indicating that there was "never" a problem; 2, "rarely" a problem; 3, "sometimes" a problem; and 4, "always" a problem.

The ET is a novel screening tool made up of seven visual analogue scales validated in patients with epilepsy. It showed a sensitivity of 85.1% and specificity of 78.8%, PPV of 0.463, and NPV of 0.961.

Patients with aggressive behavior were identified using the specific item of the AEP. Groups were compared for age, gender, age of onset and duration of the epilepsy, epilepsy diagnoses, AED treatment and combinations, seizure frequency, current depression (defined by a positive NDDIE screening), and AEP and ET scores.

Frequencies of categorical demographic and clinical variables were analyzed using the $\chi^2$ analysis or Fisher's exact test. Continuous demographic and clinical variables and AEP and ET scores were compared using the Student's t-test for independent samples or the Mann–Whitney Test according to distribution of variables. The alpha error was set at 0.05. All statistical analyses were 2-sided and conducted using the Statistical Package for Social Sciences (version 15 for Windows, SPSS Inc. Chicago, IL).

## 3. Results

From a total sample of 163 consecutive patients on LEV, 16 (9.8%) selected "always", 36 (22.1%) "sometimes", 36 (22.1%) "rarely", and 75 (46%) "never" for the AEP item on aggressiveness. Comparing patients who selected "always" against the remaining group, there was no difference in age, gender, ethnicity, duration and age of onset of the epilepsy, diagnosis, and seizure frequency (Table 1). Patients with aggressiveness were more likely to have a positive screening for depression (62.5% vs. 23.1%; Chi-square = 11,349; df = 1; p = 0.002), to have a high AEP total score (55.1 vs. 39.3; U = 418,000; p < 0.001), and to be on a polytherapy (43.8% vs. 19.8%; Chi-square = 6.762; df = 1; p = 0.034). There was no difference in specific AED combinations. Patients with self-reported aggressiveness also presented elevated scores for depression (5.7 vs. 3; U = 703,000; p = 0.007), distress (5.0 vs. 3.2; U = 808,500; p = 0.037), and anger (6.1 vs. 3.0; U = 574,500; p = 0.003) but not for anxiety (4.9 vs. 3.6; U = 940,000; p = 0.183) (Table 1).

From the other perspective, comparing patients who selected "never" against the remaining group, none of the previously identified variables were found to be associated with aggressive bhavior apart from depression (9.3% vs. 42%; Chi-square = 21,986; df = 1; p < 0.001) and AEP total score (32.6 vs. 48.0; t = −9267; p < 0.001). As variables were normally distributed in these two groups, a logistic regression model was then constructed with age and gender as potential confounders. A positive screening for depression emerged as the major associated variable with an adjusted OR of 7.1 (95% CI: 3.0–17.5; Wald = 18,537; p < 0.001).

**Table 1**
Demographic and clinical variables in study sample (total = 163).

| | SRA N = 16 (%) | Comparison N = 147 (%) | Test, 2-tailed p value |
|---|---|---|---|
| Gender | | | |
| Males | 7 (43.8) | 56 (38) | n.s. |
| Females | 9 (56.2) | 91 (62) | |
| Age, years mean ± SD | 39.9 ± 16.4 | 44 ± 15.2 | n.s. |
| Ethnicity | | | |
| White | 15 (93.8) | 109 (74.1) | n.s. |
| Black | 1 (6.2) | 14 (9.5) | |
| Asian | 0 | 16 (10.9) | |
| Mixed | 0 | 4 (2.7) | |
| Others | 0 | 4 (2.7) | |
| Age at onset, years mean ± SD | 23.4 ± 16.6 | 23.1 ± 16.6 | n.s. |
| Diagnosis | | | |
| Focal | 11 (68.8) | 97 (66) | n.s. |
| Generalized | 5 (31.3) | 45 (30.6) | |
| Unclassified | 0 | 5 (3.4) | |
| Seizure frequency | | | |
| Free | 4 (25) | 29 (19.7) | n.s. |
| 1–10/6 months | 10 (62.5) | 103 (70.1) | |
| 11–20/6 months | 1 (6.3) | 7 (4.8) | |
| >20/6 months | 1 (6.3) | 8 (5.4) | |
| AED therapy | | | |
| Monotherapy | 2 (12.5) | 59 (40.1) | Chi-square = 6.762 |
| Bitherapy | 7 (43.8) | 59 (40.1) | p = 0.034 |
| Polytherapy | 7 (43.8) | 29 (19.8) | |
| Total n AED trial, mean ± SD | 4.2 ± 1.9 | 3.8 ± 2.1 | n.s. |
| Total AEP score, mean ± SD | 55.1 ± 11.3 | 39.3 ± 12.2 | U = 418,000 p < 0.001 |
| Depression (NDDIE > 15) | 10 (62.5) | 34 (23.1) | Chi-square = 11,349 p = 0.002 |
| ET depression, mean ± SD | 5.7 ± 3.7 | 3.0 ± 3.2 | U = 703,000 p = 0.007 |
| ET anxiety, mean ± SD | 4.9 ± 3.7 | 3.6 ± 3.2 | n.s. |
| ET anger, mean ± SD | 6.1 ± 3.7 | 3.0 ± 3.2 | U = 574,500 p = 0.003 |
| ET distress, mean ± SD | 5.0 ± 3.4 | 3.2 ± 3.0 | U = 808,500 p = 0.037 |

SRA = self-reported aggressiveness "always"; AEDs = antiepileptic drugs; AEP = Adverse Event Profile; NDDIE = Neurological Disorder Depression Inventory for Epilepsy; ET = Emotional Thermometer.

## 4. Discussion

During the last 10 years, there has been increasing attention on treatment-emergent psychiatric adverse events of AEDs. This is probably due to not only the increasing number of available AEDs but also the increasing recognition of the role of comorbidities and side effects of AEDs on the quality of life of patients with epilepsy [17]. In addition, the US Food and Drug Administration (FDA) alert about an increased risk of suicide ideation and behavior in people with epilepsy treated with AEDs has clearly reinforced the need for further data in this area [18–20].

Research on behavioral effects of AEDs has a long story. The first study investigating this issue was that by Reynolds and Travers [21] who looked at serum AED levels and behavioral changes in a small group of 57 patients with chronic epilepsy and showed that patients with behavioral problems had significantly higher levels of both phenobarbitone and phenytoin than those without, irrespective of seizure frequency. Since that time, many studies investigated treatment-emergent psychiatric adverse events of AEDs suggesting that polytherapy, severity of the epilepsy, limbic system abnormalities, and a previous psychiatric history represent major risk factors [22]. The association with depression is in keeping with previous data pointing out the role of the previous psychiatric history [23,24] highlighting also the importance of the current mental state. This has been partially suggested by a recent study showing that patients reporting aggressiveness also report