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Fatigue during treatment with antiepileptic drugs: A levetiracetam-specific adverse event?

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ABSTRACT

Purpose: To examine the prevalence and clinical correlates of fatigue as an adverse event (AE) of antiepileptic drug (AED) treatment in patients with epilepsy.
Methods: Data from 443 adult outpatients with epilepsy assessed with the Adverse Event Profile (AEP) and the Neurological Disorder Depression Inventory for Epilepsy (NDDIE) were analysed.
Results: Fatigue is reported by 36.6% of patients as always a problem during AED treatment. Fatigue is more likely to be reported by females (64.8% vs. 35.2%; Chi-Square = 16.762; df = 3; p = 0.001) and during treatment with levetiracetam (42.3% vs. 33.2%; Chi-Square = 11.462; df = 3; p = 0.009). The associations with the female gender and levetiracetam treatment were not mediated by depression, as identified with the NDDIE, and could not be simply explained by the large number of subjects on levetiracetam treatment, as analogous figures resulted from the analysis of a monotherapy subsample (41.7% vs. 30.3%; Chi-Square = 11.547; df = 3; p = 0.009).
Conclusions: One third of patients with epilepsy reports fatigue as a significant problem during AED treatment. Fatigue is more likely to be reported by females and seems to be specifically associated with LEV treatment. However, fatigue is not mediated by a negative effect of LEV on mood.

1. Introduction

Adverse events (AEs) represent an important cause of treatment failure not only for early treatment discontinuation but also because they can preclude fully effective doses [1]. In addition, AEs have a negative impact on adherence to treatment [2] and quality of life [3] and represent a potential cause of disability and increased health care costs [4].

Data on AEs of antiepileptic drugs (AEDs) come from several different sources, from controlled clinical trials to open studies or uncontrolled retrospective studies and case reports. Some AEs are already expected because considered characteristic of a specific drug class (i.e. diplopia or dizziness with sodium channel blockers), while other AEs may become evident over time because they are epidemiologically rare (i.e. idiosyncratic reactions) [5] or because of increasing awareness among clinicians and researchers for a specific type of adverse event (i.e. behavioural effects of AEDs) [6]. However, in other cases AEs may not be immediately evident, unless and until patients are systematically screened for them. In fact, a cross-sectional study in adult patients with drug-refractory epilepsy has pointed out that the prevalence of AEs is around 36.5% when the assessment is based on spontaneous reporting and 95.5% when a validated screening questionnaire is used [7]. Current research has shown the importance of identifying patterns of association of AEs, highlighting the need to fully explore AEs of AEDs [8]. In fact, studies on AEs of AEDs can contribute to the understanding of the mechanisms of action of drugs that may not be immediately evident because they are not connected with their primary effect.

Fatigue is usually described as intense tiredness and can be mediated by peripheral or central mechanisms. The former refers to an inability to sustain a specified force output or work rate during exercise and originates from the cardiovascular or peripheral nervous system [9]. Central fatigue refers to a failure to initiate and/or sustain physical activities requiring attention and self-motivation, and originates from the central nervous system. Fatigue is a recognised AE of many drug classes although the underlying mechanism hasn't been fully clarified yet. In oncology, fatigue is a well-known drug-related phenomenon

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[10], occurring in the week after the cytotoxic treatment and progressively declining over the subsequent weeks [10,11]. However, fatigue has been reported with drugs other than chemotherapy agents, like statins [12] or antibiotics [13]. Data on fatigue during treatment with drugs acting on the central nervous system is limited and studies about AEDs are more than scarce as discussed by a review paper on this subject [14]. Nevertheless, some authors have reported that patients with epilepsy, especially if uncontrolled, have higher scores for fatigue than healthy controls [15]. The aim of the present paper is to document the proportion of patients reporting fatigue as an AE during AED treatment and whether this is reported by a specific subgroup of patients.

2. Methods

Data from a consecutive sample of patients with an established diagnosis of epilepsy attending the Outpatient Clinics of the Atkinson Morley Regional Neurosciences Centre, St George's University Hospitals NHS Foundation Trust in London, were analysed. As part of our routine clinical activity, all patients complete the Neurological Disorder Depression Inventory for Epilepsy (NDDIE) [16] and the Adverse Event Profile (AEP) [17,18]. As per Research Ethic Committee (REC) advice, research limited to secondary use of anonymized information previously collected during standard clinical care is excluded from formal REC review. Data storage and management was compliant with the Good Clinical Practice statement in accordance to the Declaration of Helsinki.

The NDDI-E was developed by a US Network of epilepsy specialists and it is a well-known clinical instrument for the rapid and objective detection of a major depressive episode in patients with epilepsy using a cut off score ≥15. It has been found to be a very practical and user-friendly screening instrument in an outpatient setting. The AEP was developed by Gus Baker at the Walton Neuroscience Centre in Liverpool and it is a 19-item, self-report instrument specifically developed to investigate side effects of AEDs. It is possible to analyse the scores of individual symptoms as well as calculate 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; 4 "always" problem.

Fatigue was identified using the specific subscale "Tiredness" of the AEP. Fatigue scores and categories were compared for age, gender, age of onset and duration of the disease, epilepsy diagnoses, AEDs treatment and combinations, seizure frequency and presence of depression as identified with the NDDIE. Frequencies of categorical demographic and clinical variables were analysed using the χ^2 analysis or Fisher's exact test. Continuous demographic and clinical variables and AEP scores were compared using the Student's t-test for independent samples. The alpha error was set at 0.05. All statistical analyses were 2-tailed and conducted using the Statistical Package for Social Sciences (Version 15 for Windows, SPSS Inc. Chicago, IL).

3. Results

Demographic and clinical data are shown in Table 1. From a total sample of 443 patients, 36.6% rated fatigue as "always a problem", 32.7% "sometimes", 9% "rarely" and 21.7% "never". The mean score ± SD in the total sample for the fatigue subscale was 2.8 ± 1.1.

Women rated fatigue as "always a problem" more frequently than men (females 64.8% vs. males 35.2%; Chi-Square = 16.762; df = 3; p = 0.001). The female gender association was further confirmed by the analysis of the fatigue subscale scores in the total sample as females presented significantly higher scores than males (males 2.6 ± 1.2 vs. females 3.0 ± 1.0; t = −3.567; p < 0.001). There was no correlation between age and fatigue scores in the two gender groups.

Patients with depression (DEP), as identified with the NDDIE (n = 100), presented with higher fatigue scores than those without (DEP 3.61 ± 0.62 vs. NoDEP 2.62 ± 1.16; t = 11.270; p < 0.001) and were more likely to rate fatigue as "always a problem" (DEP 66% vs. NoDEP 28%; Chi-Square = 62.993; df = 3; p < 0.001). Therefore, fatigue scores for gender were analysed again in the depressed and non-depressed groups separately to exclude a possible gender bias due to the well-known association between female gender and depression. Interestingly, the gender association was evident in the non-depressed group (males 2.34 ± 2.17 vs. females 2.82 ± 1.08; t = −3.713; p < 0.001) while depressed patients presented with globally high AEP scores and no significant gender difference was identified for the Fatigue subscale (males 3.64 ± 0.543 vs. females 3.59 ± 0.660; t = 0.465; p = 0.728).

There was no association with the age of the patient, the epilepsy type and diagnosis, the age of onset and duration of the epilepsy. There was no difference between being seizure free or not and no difference between being on a monotherapy or on a regime with two, three, or more than three AEDs. However, looking at fatigue scores for individual drugs, there was a specific association with levetiracetam (LEV) therapy. Fatigue categories for individual AEDs are shown in Fig. 1. Among patients reporting fatigue as "always a problem", most of them were on LEV (LEV 42.3% vs. NoLEV 33.2%; Chi-Square = 11.462; df = 3; p = 0.009). In addition, patients on LEV presented with higher fatigue scores (LEV = 3.0 ± 1.0 vs. NoLEV = 2.7 ± 1.2; t = 2.951; p = 0.003).

To further clarify whether the observed association with LEV treatment was simply biased by the large number of subjects taking LEV, fatigue scores were analysed in the monotherapy sample (Table 2) and again most patients reporting fatigue as "always a problem" were on LEV (LEV 41.7% vs. NoLEV 30.3%; Chi-Square = 11.547; df = 3; p = 0.009) and patients taking LEV presented with higher fatigue scores (LEV 3.18 ± 0.88 vs. NoLEV 2.64 ± 1.20; t = 3.355; p = 0.001) as compared to those taking other AEDs in monotherapy (i.e. lamotrigine, valproate and carbamazepine).

To exclude a potential confounding role of gender in the LEV group, gender distribution was analysed and there was no significant

Table 1
Clinical and demographic variables in the study sample (N = 443).

	N (%)
Gender	
Male	179 (40.4%)
Female	264 (59.6%)
Age, mean ± SD	43.1 ± 15.6
Age at onset, mean ± SD	24.6 ± 17.8
Diagnosis	
Focal	285 (64.3%)
Generalised	138 (31.1%)
Unclassified	20 (4.6%)
Seizure free	132 (29.8%)
AED therapy	
Monotherapy	213 (48.1%)
Two AEDs	160 (36.1%)
Three AEDs	52 (11.7%)
AED type	
Topiramate	37 (8.4%)
Levetiracetam	163 (36.8%)
Lamotrigine	154 (34.8%)
Pregabalin	15 (3.4%)
Carbamazepine	94 (21.2%)
Oxcarbazepine	16 (3.6%)
Gabapentin	9 (2.0%)
Lacosamide	19 (4.3%)
Phenobarbital	8 (1.8%)
Phenytoin	30 (6.8%)
Valproate	71 (16%)
Zonisamide	13 (2.9%)
Clobazam	41 (9.3%)
Total n AED failed, mean ± SD	3.2 ± 2.3
Fatigue	
Never a problem	96 (21.7%)
Rarely a problem	40 (9%)
Sometimes a problem	145 (32.7%)
Always a problem	162 (36.6%)