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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.

Key Words: epilepsy, antiepileptic drugs, adverse effects, fatigue, depression

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 amongst 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[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 $\chi 2$ 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 **Figure 1**. Among patients reporting fatigue as "always a problem", most 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 difference (Males on LEV 35.2% vs. Females on LEV 37.9%; Chi-Square=0.330; df=3; p=0.616).

To exclude a potential confounding role of depression in the association between fatigue and LEV treatment, the same analyses were repeated distinguishing between subjects with and without depression as identified with the NDDIE. As was the case in the male vs female subgroup analysis, the association of LEV treatment with fatigue was evident in the non-depressed group in both the general sample and in the monotherapy sample. In fact, in the non-depressed general sample (n=343), most subjects rating fatigue as "always a problem" were on LEV (LEV 35.3% vs. NoLEV 24.1%; Chi-Square=11.180; df=3; p=0.011) and fatigue scores were higher in those taking LEV (LEV 2.86 +/- 1.10 vs. NoLEV 2.49 +/- 1.18; t=2.875; p=0.004). Similar figures were observed in the non-depressed monotherapy sample (n=170) (LEV 3.03 +/- 0.97 vs. NoLEV 2.44 +/- 1.19; t= 3.012; p=0.004) (**Figure 2**).

As a final point, fatigue scores were compared in different AED-combinations with LEV to test the hypothesis that some combinations may be protective or detrimental. Analyses were done directly in the group of patients without depression and showed that the association with a sodium channel blocker (i.e. carbamazepine, oxcarbazepine, lacosamide, phenytoin) was not associated with high fatigue scores on LEV (**Figure 3**).

4. DISCUSSION

This is the first study looking specifically at fatigue as a potential AE of AED treatment. Our results clearly show that: i) one third of patients with epilepsy report fatigue as a significant problem during AED treatment; ii) it is more likely to be reported by females; iii) it seems to be specifically associated with LEV treatment; v) it is not mediated by an effect of LEV on mood.

Firstly, someone may argue that the item "tiredness" of the AEP does not necessarily reflect "fatigue" as a construct. In general terms, fatigue is difficult to define and measure and no single measure adequately captures the complexity of the phenomenon [19]. According to the Oxford English Dictionary "fatigue" is a synonym for "tiredness" although it is also inferred that fatigue is more severe. Given the paucity of data on this subject and the exploratory nature of our report, we found acceptable to use the item tiredness of the AEP before using more specific questionnaires. Our results clearly suggest the need for further studies on this subject using specific clinical instruments. In fact, as already stated, data on fatigue during AED treatment are inadequate. A review paper [14] on this subject showed prevalence rates for self-reported fatigue up to 33% for vigabatrin, 29% for gabapentin and 27% for LEV and speculated on the role of GABAergic neurotransmission potentiation in fatigue[14]. The hypothesis that fatigue may be mediated by an imbalance between excitatory and inhibitory neurotransmission is further supported by data coming from multiple sclerosis literature suggesting an association with glutamate blockers [20]. However, the exact mechanism beyond central fatigue is not fully elucidated. Fatigue seems to be primarily mediated by inflammation in disorders like multiple sclerosis and chronic fatigue syndrome. It has been shown that even low levels of inflammation mediators can cause functional alteration in neuronal systems including the basal ganglia, anterior cingulate cortex and

insula, all of which can modulate aspects of central fatigue [9]. It is also noteworthy that neuroimmunological disorders such as multiple sclerosis and chronic fatigue syndrome are more common in women than men [21,22] and this is thought to be due to a combination of genetic susceptibility factors and hormonal differences that affect the immune system [23]. For all these reasons, the finding in this study of a gender bias in reported fatigue is fully in keeping with current literature on central fatigue but the association with LEV is more than intriguing and it is tempting to speculate that LEV may have a central modulatory immune effect that was unknown.

Clinical trials of LEV as add-on treatment in focal epilepsies reported fatigue in up to 23% of patients [24]. A Cochrane review of 11 controlled add-on trials of LEV in drug-refractory patients showed that, despite fatigue was one of the five most common AEs, there was not an increased risk to develop fatigue over placebo [25]. A recently published study using the AEP showed that tiredness was the most common complaint in patients with epilepsy and healthy controls, but there was no difference between patients and controls [26]. In addition, a previous study comparing AEP scores in patients on monotherapy with taking CBZ, LEV, VPA, PHT or LTG did not show any difference in self-reported tiredness as "always a problem" [27]. On the other hand, a recent meta-analysis of AEs of LEV, including data from 26 randomised controlled trials, clearly showed that fatigue is one of the AEs statistically significant associated with LEV. Several factors can potentially explain discrepancies among previous studies. First, in clinical trials, fatigue is not systematically reported and distinctively identified, in fact, for example, asthenia is frequently coded as a separate entry. Second, our study shows that the association with LEV is particularly evident when patients with depression are excluded. It is, therefore, possible that, even in previous studies using the AEP, depression may have masked differences in the reporting of tiredness between different groups and among different AEDs.

The association between LEV and fatigue in non-depressed patients is particularly intriguing. A recent review paper about fatigue in epilepsy pointed out that fatigue is associated with depression [28]. We also observed that depressed patients have higher scores for fatigue as compared with non-depressed ones, but this is not surprising because patients with depression usually present with high rates of AEs in general, especially in domains like energy levels, mental speed and sleep problems [29][30]. However, our results clearly point out that the association between fatigue and LEV is not biased by a co-existing or LEV-induced depressed mood, and further confirm that fatigue is a separate entity as compared to depression. This is entirely in keeping with current psychiatric literature on distinctive neuronal networks for fatigue as compared to depression, which implicate orbitofrontal areas as well as the anterior cingulate cortex [31]. In fact, current models of fatigue hypothesize a dysfunction in the non-motor areas of the basal ganglia (i.e. ventral striatum) and their interactions with the frontal cortex and the amygdala. The effect of LEV on these specific networks is currently unknown as previous neuroimaging studies focused mainly on memory networks [32].

The effect of LEV on sleep can be another potential factor contributing to fatigue. An exploratory factor analysis of the AEP items in a large sample of patients with epilepsy showed that fatigue correlates with restlessness, upset stomach and disturbed sleep rather than with cognitive (e.g. difficulty in concentrating and memory problems) or mood items (depression, nervousness and aggression) [8]. An evidence-based review on the effect of AEDs on sleep architecture showed that LEV is a REM sleep reducer and slow-wave sleep enhancer in healthy subjects and becomes a slow-wave sleep reducer in patients with epilepsy [33]. It is quite interesting to note that the effect of LEV on sleep in patients with epilepsy has some similarities with classic GABAergic drugs like barbiturates which also are REM sleep reducers and slow-wave sleep enhancers in healthy subjects. Future studies on the

relationship between fatigue, AEDs and sleep are needed.

Finally, the favourable combination between LEV and sodium channel blockers (SCB) is of interest. In general terms, fatigue seems to be reported less frequently with SCB than with GABAergic AEDs [14]. However, whether they are protective in this regard is still unknown and should be clearly the subject of further investigations.

Our results should be considered bearing in mind the following limitations. Firstly, the retrospective design does not allow any clear causal relationship between LEV and fatigue. Secondly, the unbalanced number of patients on individual AEDs and the lack of data about AED dose and titration cannot support any causal relationship or dose-dependency. Thirdly, it is entirely possible that other AEDs, apart from LEV, are also associated with fatigue but they have not been identified as less frequently prescribed then LEV in our sample. Fourthly, it is entirely possible that other confounders, not yet identified, may account for the observed association between fatigue and LEV. However, the aim of our paper was to describe how frequently fatigue is reported by patients with epilepsy during AED treatment and whether specific associations warranting further studies were present. Our paper clearly suggests that future prospective studies on AED treatment-emergent fatigue are needed to clarify the magnitude of the problem and to confirm whether there is a specific association with LEV treatment.

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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%)
Four AEDs	18 (4.1%)
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%)

Table 2. Antiepileptic drugs in monotherapy.

Drug	**N = 213**
Topiramate	5 (2.3%)
Levetiracetam	48 (22.5%)
Lamotrigine	83 (39%)
Carbamazepine	36 (16.9%)
Oxcarbazepine	3 (1.4%)
Gabapentin	3 (1.4%)
Phenytoin	5 (2.3%)
Valproate	29 (13.6%)
Clonazepam	1 (0.5%)

Figure 1. Distribution of Fatigue item scores as presented in the Adverse Event Profile.

Figure 2. Fatigue scores in patients taking levetiracetam (LEV) as compared with the remaining subjects in the total and monotherapy samples with or without depression (DEP).

* t=2.951; p=0.003 **t=2.875 p=0.004 #t = 3.355 p =0.001 ##t= 3.012; p=0.004

Figure 3. Percentage of patients reporting fatigue as "always a problem" in patients with or without levetiracetam (LEV) in combination with sodium channel blockers (NaCB).

*Chi Square 13.134 df=3 p=0.004