Epilepsy & Behavior 75 (2017) 237–240

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Effect of sleep patterns on levetiracetam induced mood changes☆

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ARTICLE INFO

Article history:
Received 30 May 2017
Revised 15 July 2017
Accepted 19 July 2017
Available online 18 August 2017

Keywords:
Levetiracetam
Sleep
Mood
Depression
Anxiety
Seizure
Epilepsy

ABSTRACT

A common side effect of levetiracetam is the onset of neuropsychiatric symptoms such as mood changes including depression, anxiety, agitation, and sometimes psychosis. We performed a retrospective analysis to examine the effect of sleep pattern and chronotype on individual susceptibility to levetiracetam-induced mood changes. We reviewed records of 110 adults with epilepsy presenting to our clinic during a 3-month period, and categorized them into those currently on levetiracetam, and those no longer taking it because of mood-related adverse effects. Patients were administered Morningness–Eveningness Questionnaire (MEQ), Beck's Depression Inventory-II, and Neurological Disorders Depression Inventory in Epilepsy. Using various statistical methods, we analyzed the comparison of these 3 different scales amongst one another and between those subjects who tolerated levetiracetam and those who did not. Of 110 patients, 74 (67%) tolerated levetiracetam and 36 (33%) did not tolerate it because of mood changes with chronotype being a significant determining factor. Of those who tolerated the drug, 62% were intermediate chronotypes and 20.3% and 17.6% were morning and evening chronotypes, respectively. For those intolerant, 86.1% were morning chronotypes, 13.9% were intermediate chronotypes, and none were evening chronotypes ($p < 0.001$). Thirty-two percent of morning chronotypes, 100% of evening chronotypes, and 90.2% of intermediate chronotypes were tolerant of levetiracetam ($p < 0.001$). Chronotype significantly affected toleration of levetiracetam. Chronotype, but not depression, was a significant factor in determining tolerability of mood-altering side effects of levetiracetam, via statistically significant trend for an increasing ability to tolerate levetiracetam as chronotype would shift from morning to intermediate to evening. Additional research may help establish if this is related to possible underreporting of poor mood with evening chronotypes, and morning chronotypes having more stringent sleep schedules, genetic factors, or other reasons.

1. Introduction

Levetiracetam is one of the safest and most widely used anticonvulsants. The most frequently encountered and troubling side effect is the onset of neuropsychiatric symptoms such as mood changes of depression, anxiety, agitation, and sometimes psychosis [1,2]. This causes problems for patients and their family members, and often necessitates discontinuation of the medication. The ability to predict which patients will not tolerate levetiracetam would have a major impact on clinical decisions to successfully treat epilepsy.

Chronotype refers to the circadian rhythm of a given organism that determines if alertness and productivity are greater in the hours of early morning or later in the day [3]. When identifying a chronotype, three broad categories are often used: Morning type (informally known as "Lark"), Evening type (informally known as "Owl"), and Intermediate type [4]. The purpose of this study was to determine if there is a relationship between a patient's sleep pattern, i.e., chronotype, and their susceptibility to the mood deteriorating side effects of levetiracetam. We hypothesize that the individual chronotype may predict tolerance of the medication.

In his thesis *Charting Individual Daily Rhythms* [5], O. Oquist from University of Goteborg, Sweden, Department of Psychology, introduced a questionnaire with the aim to separate "morningness" and "eveningness" [6]. This questionnaire was modified by Ostberg and Horne, who in 1976 had published the 19-item Morningness–Eveningness (ME) Questionnaire (MEQ) [4], which has been widely used in medical research. The scoring for the MEQ consists of a scale from 16 to 86, based on which an individual is determined to have one of five chronotypes: Definite Evening, Moderate Evening, Intermediate, Moderate Morning, or Definite Morning [Table 1].

There is accumulating research suggesting a link between chronotype and mood. Some studies show higher association with depression or

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http://dx.doi.org/10.1016/j.yebeh.2017.07.038
1525-5050/

Table 1
Morningness–Eveningness Questionnaire scoring.

Score	16–30	31–41	42–58	59–69	70–86
Chronotype	Definite Evening	Moderate Evening	Intermediate	Moderate Morning	Definite Morning

mood fluctuation in evening types, in the general population [7]. However, we suggest that since levetiracetam may cause increased sleepiness, morning types are more susceptible to mood and behavior effects since morning chronotypes sleep less overall [8,9].

Neurologists often utilize screen tools such as the Beck's Depression Inventory-II (BDI-II) and the Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) to screen for depression and anxiety in clinical practice. We use these inventories to measure the presence and/or degree of mood problems in our epilepsy population.

The BDI-II is one of the most widely used depression screening instruments used by clinicians and is in accordance with the depression criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). It consists of 21 items to assess for the presence and degree of depression in patients, with each item containing lists of 4 statements arranged in increasing severity about a particular depressive symptom [10]. Scoring for the BDI-II [Table 2] consists of a scale from 0 to 63, which corresponds to one of four severities of depression, including Minimal, Mild, Moderate, and Severe.

The NDDI-E is a validated, rapid, self-rating, 6-item questionnaire for depression screening in patients with epilepsy [11]. Each item has an option for the patient to select one of 4 options (Never, Rarely, Sometimes, and Always or Often) with each respectively being scored from 1 to 4 [Table 3]. Scores of greater than 15 on the NDDI-E are suggestive of a diagnosis of depression.

2. Methods

2.1. Study design

We reviewed the electronic records of patients with epilepsy who presented for follow-up at Cooper University Hospital's Neurology clinic during a 3-month period in 2016, in a sequential fashion. Inclusion criteria were adults with a diagnosis of epilepsy, ages 18 years and older, either taking levetiracetam currently or had taken it prior yet had to stop because of intolerable side effects, i.e., depression and/or anxiety. Exclusion criteria were diagnosis of developmental delay with intellectual disability or IQ < 70, a prior diagnosis of a mood disorder, or psychiatric diagnosis and on antipsychotic medication (prior to levetiracetam), presence of a sleep disorder, or having a diagnosis of dementia.

Out of 110 subjects, all had completed an MEQ, 91 had also completed a BDI-II, and 101 had also completed an NDDI-E. These questionnaires were being administered to the patients prior to the study's inception. Extracted data included the subject's age, gender, whether or not actively taking levetiracetam, MEQ scale, BDI-II score, and NDDI-E score. For our study, we combined Definite Evening and Moderate Evening Chronotypes into "Evening Chronotype" and Definite Morning and Moderate Morning Chronotypes into "Morning Chronotype".

Table 2
Beck Depression Inventory-II scoring.

Score	Range
0–13	Minimal
14–19	Mild
20–28	Moderate
29–63	Severe

Table 3
Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) scoring.

	Always or Often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

An NDDI-E score of greater than 15 is suggestive of a diagnosis of depression.

2.2. Statistical analysis

There were three analyses done for this study: the comparison of the different scales (Morningness–Eveningness scale, BDI score, and NDDI score), the comparison between those who tolerated levetiracetam and those who did not, and the comparison between those who were classified as morning individuals and intermediate and evening individuals. The correlation of the different scales was figured by the Pearson and Spearman Rho Correlations. The analysis comparing factors by those who tolerated levetiracetam vs. those who did not were completed by using the independent t-test, Mann–Whitney U test to compare continuous factors (age and scores), and chi square tests to compare categorical factors.

We used the MEQ and categorized those who were morning individuals vs. intermediate vs. evening individuals within our sample. When we compared those individuals with morning vs. evening characteristics (excluding those who were intermediate), we used independent t-tests, Mann–Whitney U test, and chi square tests. When we compared the factors between these three groups (including the intermediate group), we used One Way ANOVA to compare the means of the continuous variables and chi square tests to compare the proportions of categorical variables. We also used chi square tests to compare other scale ranges in the different analysis. For BDI-II, we categorized the score by minimal, mild, moderate, and severe depression, and for NDDI, we dichotomized by labeling one category "depressed" and the other category "not depressed". These were compared between those who tolerated levetiracetam vs. those who did not and those who were morning vs. evening (vs. intermediate). The protocol was approved by the Cooper Health System Institutional Review Board.

3. Results

Scores were collected for 110 patients. Of these, 74 (67%) tolerated levetiracetam, and 36 (33%) did not tolerate it because of mood changes [Table 4]. Chronotype was a significant factor in determining toleration

Table 4
Association of factors with tolerability of levetiracetam.

Factor	Levetiracetam tolerated		Levetiracetam not tolerated		p value
	N		N		
Age (mean/SD)	74	43.81 (17.10)	36	47.56 (17.65)	0.289
Gender — male (n/%)	74	38 (51.3%)	36	14 (38.9%)	0.219
BDI-II (median/SD)	60	5 (1–13.75)	31	8 (4–14)	0.234
BDI-II (n/%)	60		36		0.057
Minimal		45 (75%)		21 (67.7%)	
Mild		6 (10%)		7 (22.6%)	
Moderate		2 (3.3%)		3 (9.7%)	
Severe		7 (11.7%)		0 (0%)	
NDDI (mean/SD)	68	11.06 (4.60)	33	11.15 (3.47)	0.919
NDDI — depressed (n/%)	73	10 (14.7%)	36	14 (38.9%)	0.246
MEQ (n/%)	74		36		<0.001
Morning		15 (20.3%)		31 (86.1%)	
Evening		13 (17.6%)		0 (0%)	
Intermediate		46 (62.2%)		5 (13.9%)	