SHORT COMMUNICATION

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# Interictal Dysphoric Disorder in Epilepsy and Its Relationship with Specific Clinical and Demographic Variables

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**ABSTRACT**

Patients with epilepsy present a variety of psychiatric comorbidities, with mood disorders and anxiety disorders as well as interictal dysphoric disorder as the most frequent and often associated with comorbid mental conditions. Interictal dysphoric disorderand ictal and peri-ictal changes may contribute to overall clinical symptomatology in epilepsy, as well as subjective and objective adverse effects of anti-epileptic drugs. We performed a post-hoc analysis to verify the relation of interictal dysphoric disorder with specific clinical and demographic variables in people with epilepsy, including the correlation between interictal dysphoric disorder and anti-epileptic drugs. We found no correlation between the incidence of interictal dysphoric disorder and drug-resistant epilepsy, and no correlation between the incidence of interictal dysphoric disorder and sex was observed. The results of our analysis indicate that patients with interictal dysphoric disorder, compared with those with no interictal dysphoric disorder, had epilepsy onset at a later age, had had a history of psychiatric treatment and had distinctly lower, but not statistically significant, percentage of active employment status. Another finding was the frequent suicide attempts in people with epilepsy (11.5%). However, there was no relationship with interictal dysphoric disorder. We also did not find any evidence supporting the impact of epileptic medication on the incidence of interictal dysphoric disorder nor did the data contribute to support the evidence of interictal dysphoric disorder as a standing-alone phenomenon. An essential issue in epilepsy is awareness and understanding of interictal dysphoric disorder and concomitant mental health abnormalities as this is crucial for clinical practice and may significantly determine the progression and management of epilepsy if it remains ignored, and hence lead to a severe decline in life quality.

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## INTRODUCTION

Patients with epilepsy present a variety of psychiatric comorbidities that include mood disorders and anxiety disorders, with a pool prevalence of 20.2% and 22.9%, respectively.[1] One of the key diagnostic concepts in epilepsy associated with psychiatric comorbidity is interictal dysphoric disorder (IDD),[1-3] a term coined by Blumer et al.[2] Some authors consider IDD as a set of symptoms that is less epilepsy-related than it was postulated initially,[4,5] hence the IDD concept itself and also its relation to epilepsy has been put into discussion. There are 8 symptoms characteristic of IDD, all of them grouped into 4 labile depressive symptoms (anergia, insomnia, depressed mood, and pain), 2 labile affective symptoms (fear and anxiety), and 2 specific symptoms (paroxysmal irritability and euphoric moods). It is estimated that standardized classification systems like the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) still fail to recognize up to 50% of people with epilepsy (PWE) with atypical psychiatric symptoms that are comparable to IDD characteristics.[6] The increasing data supported the hypothesis that neuroinflammatory processes within the brain constitute the pathophysiology of both epilepsy[7,8] and affective disorders, including suicidal behaviors.[9] Ali N. Kamali *et al*[7] postulate the involvement of neuroinflammation in the pathophysiology of epilepsy, and the link between recurring seizures of epilepsy and higher levels of immune mediators that seem to play a vital role in initiating them.

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The authors propose immune mechanisms to be playing a vital role in some epilepsies, as well as systematic immune disorders (including SLE, Sjögren's syndrome, and autoimmune vasculitis) that have been reported to lead to seizures and epilepsy.[7] Apoptosis and neuroinflammation have been observed in the temporal lobes of drug-resistant epilepsy (DRE) patients, and these findings imply that neuroinflammation, which can result in extrinsic apoptosis in the epileptic focus, is accompanied by intense tumor necrosis factor (TNF) expression in the brain and elevated levels of TNF, interleukin (IL)-7, and IL-4 in the blood serum.[8] The key conclusions of a systematic study by Serafini et al[9] indicate that neuroinflammation may be relevant to the pathophysiology of suicidal behavior. Pro-inflammatory cytokines like IL-1, IL-2, IL-6, interferon (IFN), and TNF, as well as anti-inflammatory cytokines like IL-4 and IL-10, have been shown to be out of balance in both suicidal and untreated depressed patients.[9] The most common comorbidity in PWE is depression, with prevalence rates ranging from 20.2%[10] to 44% in PWE and reaching 54% in refractory epilepsy. Epilepsy is not only linked to a higher likelihood of developing depression, but depression is also positively correlated with the severity of epilepsy. In PWE, depression is linked to reduced anti-epileptic drug (AED) tolerance, a lower quality of life, and an increased risk of suicide. Suicidal thought is most frequently triggered by the presence of depressive symptoms, which also have a detrimental effect on social functioning and mean quality of life (QoL).[11] Both epilepsy and depression can affect a person's social interactions, interpersonal communication, and the likelihood of unexpected episodes.[11,12] According to certain research, epilepsy and depression are linked in a bidirectional manner[11,12] by epilepsy surgery, adherence to AEDs, and a rise in the likelihood of DRE, particularly in newly diagnosed PWE.[11,12] Therefore, the implementation of proper psychiatric treatment of depression in PWE is crucial in the management of epilepsy. A one-third of patients who use antidepressants do not respond effectively to the medication or achieve a full remission, despite the fact that there are numerous pharmacological treatments for depression.[13] Major depression, treatment-resistant depression (TRD), non-suicidal self-injury (NSSI), and suicidal conduct may all need the use of Buprenorphine (BUP). Several studies show that BUP, even in patients with TRD is a safe, efficient method for reducing severe suicidal thoughts and symptoms of depression and behaviors such as non-suicidal self-injury (NSSI), when used at low dosages.[13] Due to the significant comorbidity of psychiatric diseases, particularly IDD, that epilepsy is linked to, the study's primary goal was to examine the prevalence of IDD and pharmacological treatment by the reanalysis of data from a study sample of PWE. Additionally, because behavioral issues in epilepsy may affect how both medical conditions progress, we put a particular focus on a possible relationship between DRE and the diagnosis of IDD. We also investigated a possible relationship between gender and diagnosis of IDD. As a secondary objective, we put forward a hypothesis that IDD is a stand-alone nosographic phenomenon.

**MAIN POINTS**

- The prevalence of interictal dysphoric disorder (IDD) in the sample group was high (48.5%), and 72.9% of the patients were diagnosed with interictal dysphoric disorder (DRE).
- We found no correlation between the incidence of IDD and DRE, as well as no correlation between the incidence of IDD and sex was observed.
- Patients with IDD had a later age of epilepsy onset compared to those without IDD and more often had a history of psychiatric treatment.

## MATERIAL AND METHODS

### Participants

This work analyzes data generated as part of a registry reported elsewhere.[14,15] Of 118 consecutive PWE from a tertiary epilepsy center evaluated, 96 were enrolled. According to the International League Against Epilepsy criteria,[9,16] the included individuals were between the ages of 18 and 65, had active epilepsy, and had been receiving stable anti-epileptic medication for 2 months before the trial. The exclusion criteria included having had a seizure within the previous 24 hours of the examination, having had more than 10 seizures in the previous month (to reduce the potential impact of ictal and peri-ictal psychiatric symptoms), having undergone neurosurgery, or having a history of severe brain injury as determined by neuroimaging. The exclusion criteria also included psychiatric interview findings of antisocial/borderline personality disorder (PD), mental retardation, drug and/or alcohol use or abuse during the last 6 months, and the presence of pseudo-seizures (psychogenic non-epileptic seizures). A psychiatric interview was used to determine whether a patient had an antisocial or borderline PD and other exclusion criteria such as pseudo-seizures (psychogenic non-epileptic seizures), mental retardation, drug or alcohol abuse, or dependence in the previous 6 months. The Ethic Research Committee of the Medical University of Gdansk approved the study (protocol code NKEBN/568/2006/2007, approved on February 5, 2007), and it was carried out in accordance with the Declaration of Helsinki. For each participant in the study, written informed consent was collected.

### Measures

The Structured Clinical Interview for DSM-IV-TR Axis I Disorders was used to diagnose all participants by the same researcher (MSW) during a single study visit (SCID-I). Information about the patients' sociodemographic status and medical history was gathered through a structured interview, and information about a person's gender, age,

marital status, financial circumstances, age at which seizures began, type and frequency of seizures, auras experienced, length of epilepsy, length of therapy, mental history, and presence of lesions was taken into account. For the majority of patients, the findings of laboratory tests, electroencephalograms, and computed tomography/magnetic resonance imaging were available. Records from the epileptologist's referral source were used to confirm the data. In order to conduct analysis for this study, the participants were categorized into a thorough diagnostic group for anxiety and depressive disorders.

### Statistical Analysis

Shapiro–Wilk test was used to assess the normal distribution of continuous data and Mann–Whitney *U* test was for non-normally distributed data. Descriptive statistics of the data are presented with n (%) and, for non-normalized variables, are shown as median (IQR). Pearson's chi-square and Fisher–Freeman–Halton exact test were used for categorical data. $\alpha$ = 0.05 was taken as the level of significance. Statistical procedures were performed using Statistica 10.0.1011. (TIBCO Software Inc.; StatSoft, USA).

## RESULTS

The majority of the study group (n = 96) were females (n = 65, 68%), almost one-half of the participants were diagnosed with IDD (n = 47, 48.5%) and 70 (73%) of patients were diagnosed with DRE. Almost half of the studied group (n = 46, 47.9%) required polytherapy with AEDs (Table 1, *P* = .845). Psychopharmacological treatment was applied in 6 patients (6.3%) (Table 2). We found no relationship between the incidence of IDD and DRE (Table 1, *P* = .901) as well as between the incidence of IDD and sex (Table 1, *P* = .426). The results of our analysis indicate that the group of patients with IDD, compared with those not diagnosed with IDD, is characterized by late epilepsy onset (Table 1, *P* = .033), and higher incidence of psychiatric comorbidity (Table 1, 12/47, 25.5% vs 4/49, 8.2%; *P* = .022). The lower percentage of active employment in the IDD group (12/47, 25.5%) compared to the non-IDD group (20/49, 40.8%) does not reach statistical significance (*P* = .112).

**Table 1.** Demographic and Clinical Characteristics and the Presence of Interictal Dysphoric Disorder

| | Median (IQR) | | | *P* |
|---|---|---|---|---|
| | All Patients (n = 96) | IDD (+) (n = 47) | IDD (−) (n = 49) | |
| Demographic characteristics | | | | |
| Age | 36 (21) | 40 (20) | 32 (21) | .278 |
| Education, in years | 12 (0) | 12 (0) | 12 (0) | .507 |
| Epilepsy-related characteristics | | | | |
| Age of epilepsy onset | 16 (14) | 20 (19) | 16 (12) | .033 |
| Duration of epilepsy | 16.5 (18.5) | 14 (19) | 20 (17) | .228 |
| Number of seizures/last month | 2 (4) | 2 (4) | 2 (3) | .235 |
| | n (%) | | | |
| Number of patients, n (%) | 96 (100) | 47 (48.96) | 49 (51.04) | |
| Demographic characteristics | | | | |
| Male sex | 31 (32.29) | 17 (36.17) | 14 (28.57) | .426 |
| Employment status | | | | |
| Employed | 31 (32.29) | 12 (25.53) | 20 (40.82) | .112 |
| Unemployed | 65 (67.71) | 35 (74.47) | 29 (59.18) | |
| Partner relationship | | | | |
| Stable | 70 (72.92) | 34 (72.34) | 36 (73.47) | |
| Single/divorced | 26 (27.08) | 13 (27.66) | 13 (26.53) | .901 |
| Etiology of epilepsy | | | | |
| Symptomatic | 69 (71.88) | 33 (70.21) | 36 (73.47) | |
| Idiopathic | 19 (19.79) | 11 (23.40) | 8 (16.33) | .588 |
| Genetic | 8 (8.33) | 3 (6.38) | 5 (10.20) | |
| Drug resistant | 70 (72.92) | 34 (72.34) | 36 (73.47) | .901 |
| Polytherapy | 46 (47.92) | 23 (48.94) | 23 (46.94) | .845 |
| History of psychiatric treatment | 16 (16.67) | 12 (25.53) | 4 (8.16) | .022 |
| Suicidal attempts in the past | 11 (11.46) | 6 (12.77) | 5 (10.20) | .694 |

IDD, interictal dysphoric disorder; IDD (+), patients with IDD diagnosis; IDD (−), patients with no IDD diagnosis; IQR, interquartile range.

## DISCUSSION

Out study revealed a high prevalence of IDD in PWE. From all the studies in the field of IDD and epilepsy, only 2 studies revealed a similar high prevalence of IDD in PWE (63.3% and 88%).[18,19] The mean prevalence found in other studies was much lower (19%).[4]

In our study, we observed a high prevalence of IDD, but it was not positively related neither to gender (females) nor to DRE, and our findings are inconsistent with other studies.[3,20-22] It is suggested that the female gender is affected by epilepsy in a greater proportion than male,[23] but the data on plausibility of DRE in females is conflicting.[23,24]

As a secondary objective, we put forward a hypothesis that IDD is a stand-alone nosographic phenomenon, but the data did not contribute to support the evidence of IDD as a standing alone phenomenon. Based on the current studies available up to date, it is difficult to validate IDD as a distinct nosological category and concerns exist about the classification of IDD as a separate nosological entity. Zinchuk et al[18] found no IDD specificity for epilepsy, suggesting that IDD symptoms may relate to severe major depressive disorder (MDD) and anxiety distress. No IDD prevalence differences were observed between epilepsy

**Table 2.** Clinical Treatment-Related Variables in the Study Group with People with Epilepsy (n = 96)

| Pharmacological Treatment | n (%) |
|---|---|
| **Treatment with AEDs** | |
| Carbamazepine | 52 (54.17) |
| Valproic acid | 32 (33.33) |
| Lamotrigine | 24 (25) |
| Topiramate | 13 (13.54) |
| Oxycarbamazepine | 7 (7.29) |
| Tiagabine | 7 (7.29) |
| Vigabatrin | 5 (5.21) |
| Phenytoin | 3 (3.13) |
| Phenobarbital | 3 (3.13) |
| Clonazepam | 2 (2.08) |
| Gabapentin | 2 (2.08) |
| **Psychopharmacological treatment** | |
| Antidepressants | 6 (6.25) |
| Antipsychotics | 1 (1.04) |
| Benzodiazepines | 1 (1.04) |
| NONE | 89 (92.71) |

AEDs, anti-epileptic drugs; DRE, drug-resistant epilepsy.

patients with MDD and those with MDD alone. Amiri et al[4] questioned IDD's existence as a separate entity due to the lack of reliable identification tools. Labudda et al[5] reported similar IDD frequency and symptom clusters in psychiatric samples, with most IDD-diagnosed epilepsy patients having a history of psychiatric diagnoses, primarily anxiety and depression disorders. This indicates there is a significant overlap between DSM Axis I diagnoses and IDD. The authors propose a prospective redefinition of IDD, diagnosing it only in people without psychiatric disorders. It is questionable, though, whether IDD should be regarded as a distinct entity unique to epilepsy patients without concurrent psychiatric disorders because IDD is frequently accompanied with comorbid PDs in epilepsy, such as mood or anxiety disorders.[1,3] The most common psychiatric comorbidity among patients with epilepsy involves both mood and anxiety disorders (with a frequency of 20.2% and 22.9%, respectively);[10] however, IDD as well as ictal and peri-ictal features may contribute to overall clinical symptomatology in epilepsy.[25-27] The clinical picture of epilepsy symptoms manifestation also includes subjective and objective adverse effects of AEDs.[3,28] Anti-epileptic drugs have long been known to have a profoundly negative impact on cognitive abilities, especially when used in polytherapy. The causes of cognitive side effects that develop during treatment are multifaceted, with several factors being involved, such as gender, age, baseline cognitive performance as well as the presence of brain pathology, the occurrence of psychiatric comorbidities, onset and duration of disease, and pathophysiology of the brain disorder.[29] Early onset of epilepsy and hence long-term AEDs treatment may both contribute to cognitive impairment considering psychiatric comorbidity that frequently goes along with epilepsy.[10,30-31] All those factors together may significantly impair clinical and psychosocial functioning.[29] The data indicate a high prevalence of IDD in chronic central nervous system disorders as well,[1,25,32] not only in patients with drug-refractory temporal lobe epilepsy with mesial temporal sclerosis,[21] suggesting that IDD may occur not only specifically in PWE. In a study by Suda et al,[3] patients without IDD were compared to patients with IDD and the latter had extraordinarily high rates of mood disorders (68.0% vs. 20.4%), anxiety disorders (52.0% vs. 12.6%), and psychotic disorders (48.0% vs. 10.7%) comorbidity. The authors hypothesized that IDD had a strong correlation with comorbid mental disorders (PDs), earlier-onset epilepsy, refractory complex partial seizures (CPS), psychotropic drug use, subjective adverse effects of AEDs, and subjective depression.[3] There are a few confounding factors that should be considered in relation to the IDD phenomenon and epilepsy itself, including variations in study populations, the high rate of mental comorbidity, and the use of psychometric tools that may potentially lead to bias.[33] Drug-resistant epilepsy is frequently accompanied with severe psychiatric comorbidities, with anxiety and depression disorders being the most prevalent.[22,34] In a study by Nogueira et al,[34] 68.3% of patients with drug-resistant Mesial temporal lobe epilepsy revealed symptoms of anxiety or depression. Those with mixed MD/AD had their seizure frequency significantly higher. Another study[22] revealed high comorbidity of anxiety and mood disorders, including IDDs, in a 52.9% population of people with focal epilepsy who are medication resistant.

This study has certain significant limitations that should be recognized. The PWE sample, which did not include a control group of healthy adults but may be representative of the general population, underwent a post hoc analysis. The findings of this study therefore only apply to the PWE group and cannot be used to generalize about the public. The small PWE sample size and potential bias in selection are additional study limitations because the tertiary reference center was linked to an increased probability of difficult epilepsy courses. Although patients with more than 10 seizures in the previous month and those whose most recent seizure occurred within 24 hours of the assessment were excluded, the clinical presentation of an anxiety disease may be mistaken for seizure manifestations. A further disadvantage is the potential for ictal or postictal anxiety, which can appear within 72 hours of a seizure and needs to be distinguished from the classification of anxiety disorder. At the clinical interview, the aforementioned circumstances were partially eliminated as confounding. No test-retest reliability analysis was done to assess whether the test findings were consistent because the study procedures were carried out throughout a single visit to the interview site by a single rater. As a result, it is possible that the observations are

distorted and that no inferences may be derived about the instrument's long-term stability and dependability. Regarding the agreement between psychometric results, the independent raters might have lessened the inflation bias. There was also no non-epileptic neurological disorder control group or a control group of people suffering from anxiety or mood disorders not related to epilepsy. Another key study constraint is psychiatric assessment with SCID-I for DSM-IV-TR, which has been updated to version 5 (SCID-5-CV for DSM-5). The diagnosis rates and the resulting prediction values could be impacted using an out-of-date instrument. However, given the profile of diagnoses for anxiety disorders in the study group, we predicted that this would not significantly affect the findings of our investigation. The findings of the study cannot be applied to the entire PWE population due to these constraints taken combined.

nterictal dysphoric disorder was found to be very prevalent (49%) in the study sample; however, we did not find a correlation between the incidence of IDD and DRE, and no correlation between the incidence of IDD and sex was observed either. Although it may be the part of the medication the patients receive, we do not find any evidence in support of the impact of epileptic medication on the incidence of IDD. However, further research is needed. It may be hypothesized that IDD is a stand-alone phenomenon not related to epilepsy, implicating further research in this field; however, data do not contribute to support evidence of IDD as stand- alone thing. A substantial comorbidity between psychiatric illnesses with epilepsy exists including IDD, and recognition as well as implementation of proper psychiatric treatment is a clinically significant issue. Not only epilepsy but also chronic affective symptoms may negatively impact the patient's quality of life. We still lack evidence-based recommendations and, for example, placebo-controlled research on the treatment of psychiatric disorders in epilepsy, except of one focusing on to the management of depression in epilepsy. There are not enough studies on how anti-epileptic medications may affect the course of comorbid psychiatric disorders, and considering a high comorbidity of mood disorders, IDD, as well as increased irritability and impulsiveness, and hence, increased risk of suicide in PWE, more studies are needed in this field, including improvement of diagnostic tools to facilitate a better distinction among other psychiatric diseases and interictal dysphoric disorder. An essential issue in epilepsy is awareness and understanding of IDD and concomitant mental health abnormalities as this is crucial for clinical practice and may significantly determine the progression and management of epilepsy if remains ignored and hence lead to a severe decline in life quality.

**Ethics Committee Approval:** This study was approved by Ethics Committee of Medical University of Gdansk (Approval No: NKEBN/568/2006/2007, Date: 2007-02-05).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

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