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Relationships of depression and anxiety symptoms with seizure frequency: Results from a multicenter follow-up study

Lorenz B. Dehn[a,b,*], Margarete Pfäfflin[a], Sabine Brückner[c], Martin T. Lutz[c], Bernhard J. Steinhoff[d], Thomas Mayer[c], Christian G. Bien[a], Fridtjof W. Nussbeck[b], Theodor W. May[a,b]

[a] Society for Epilepsy Research, Bethel Epilepsy Center, Bielefeld, Germany
[b] Department of Psychology, Bielefeld University, Bielefeld, Germany
[c] Saxonian Epilepsy Center Radeberg, Radeberg, Germany
[d] Kork Epilepsy Center, Kehl-Kork, Germany

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ABSTRACT

Purpose: Depressive and anxiety disorders are frequent among people with epilepsies. There are, however, only few longitudinal studies, which examine the relationship between these comorbid psychiatric disorders and epilepsy-related variables. Thus, we investigated the interrelationships of depression and anxiety symptoms with seizure frequency across time.

Methods: Before admittance to an epilepsy center (T1) and six months after discharge (T2), patients (n = 198) with mainly difficult-to-treat epilepsies completed the *Hospital Anxiety and Depression Scale* (HADS). Correlation and path analyses were conducted.

Results: Depression and anxiety symptoms (HADS) as well as seizure frequency significantly decreased from baseline to follow-up. Both at T1 and T2, seizure frequency was slightly, but significantly correlated with depression and anxiety levels (r_s = 0.17–.32). Cross-lagged-analyses showed that baseline (T1) level of depression significantly predicted frequency of seizures at follow-up (T2). However, anxiety at T1 was not a significant predictor of seizure frequency at T2 and seizure frequency at T1 did not predict either depressive or anxiety symptoms at T2.

Conclusion: The present findings emphasize the importance of psychiatric comorbidities, especially depression, for seizure frequency and its progress in patients with difficult-to-treat epilepsies referred to a specialized epilepsy center. Thus, comorbid psychiatric disorders need specific consideration as part of a comprehensive diagnostic and therapeutic treatment approach.

1. Introduction

People with epilepsies (PWE) show an increased prevalence of comorbid depressive and anxiety disorders with frequencies between 30% (in population-based samples) and 50% (in therapy-resistant samples) [1,2]. In order to detect and treat depression and anxiety disorders in PWE [3,4], it is important to reveal and investigate variables associated with their modulation or with an increased risk for their development. Reviewing psychosocial predictors of depression and anxiety in PWE Gandy et al. [5] remarked: *"Although cross-sectional studies are an important step for identifying predictors, they are limited to correlational inferences, such that causation cannot be inferred"* (p. 229). So far, there are only few longitudinal studies examining the relationship between depression and anxiety with different influencing variables over time.

Endermann [6] examined 77 patients regarding different variables at their admission to an epilepsy center. Using regression analytical methods, the effectiveness of antiepileptic drugs (AED) rated by the physicians and the depressive symptoms at admission (Z-D, Zerssen's D-scale) predicted 48% of variance of depression at discharge.

Reisinger and Dilorio [7] also used multiple regression analyses for prediction of depressive symptoms (CED, Center for Epidemiological Studies – Depression Scale) by different baseline variables at study begin as well as after three and six months follow up. In a sample of 319 inpatients, employment status, social support, and epilepsy-related stigma emerged as predictors of depression

* Corresponding author. Present address: Evang. Hospital Bethel, Clinic of Psychiatry and Psychotherapy, Research Division, Remterweg 69–71, 33617 D–Bielefeld, Germany.
E-mail address: lorenz.dehn@evkb.de (L.B. Dehn).

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scores at all three time points. However, the regression models did not control for baseline depression and no measure of seizure frequency was included, although it has been found to be associated with depression in prior studies [8,9].

Thapar et al. [10] explicitly examined the interrelationship between depressive symptoms and seizure frequency in a community-based sample (n = 976). All PWE were sent questionnaires, including the Hospital Anxiety and Depression Scale (HADS) to assess depression symptoms, and the Liverpool Quality of Life questionnaire, from which the information on seizure frequency (none,<1/month, ≥1/month) was taken. The authors found that depressive symptoms and seizure frequency were predictors of each other at both time points one year apart. Furthermore, cross-lagged analysis showed that depression scores at the first assessment predicted seizure frequency at the second assessment and, vice versa, seizure frequency at the first assessment predicted depression scores at the second assessment. This result demonstrated a bidirectional interrelationship between the two variables.

In a further study with PWE from general practices (n = 433), Thapar et al. [11] reported that baseline depression scores (HADS-D) predicted a change in seizure recency (time since last seizure) and frequency after five months. A predictive association was also demonstrated for baseline anxiety symptoms (HADS-A) and a five months later change in seizure recency and frequency, but it was mediated by depression. The reversed prediction of anxiety symptoms through baseline seizure frequency has not been considered further.

1.1. Aim of this study

Patients referred to an epilepsy center are predominantly characterized by long-lasting, difficult-to-treat epilepsies. Improving seizure control is a main treatment goal, e.g. by modifying the AED regime [12]. A majority of these patients also exhibits psychiatric comorbidities, which could compromise quality of life and treatment response [13]. As a secondary analysis of data gained in a broader epilepsy center evaluation survey [14], the present study examined the interrelationships between depressive or anxiety symptoms and seizure frequency before and after inpatient treatment. Given the recent discussion on reproducibility difficulties in science [15,16], we wanted to re-examine and extend the results of Thapar et al. [10] in a sample of epilepsy inpatients. We hypothesized that a) patients' depression level prior to treatment predict seizure frequency subsequent to discharge and vice versa as well as b) anxiety symptoms at admission predict seizure rates after inpatient treatment and vice versa.

2. Methods

2.1. Patients

Four German diaconal epilepsy centers (Bethel, Bielefeld; Hephata, Schwalmstadt-Treysa; Kork, Kehl-Kork; and Kleinwachau, Radeberg) consecutively included patients, according to the following criteria: planned inpatient, non-surgical treatment because of a verified epileptic disorder, age ≥16, able to answer questionnaires independently or with assistive support. Patients with only non-epileptic seizures, insufficient German language skills or cognitive impairments, which constrain the completion of questionnaires, were excluded. The ethics committee of the University of Muenster, Germany, approved the study protocol.

2.2. Study design and procedure

The underlying evaluation survey was carried out as a prospective, multicenter, pre-post-design study [14]. Patients were asked to complete a questionnaire, send by mail, before admission to the center (T1, pre-measurement) and also 6 months after discharge (T2, follow-up).

2.3. Instruments

2.3.1. Depressive and anxiety symptoms

Depressive and anxiety symptoms were assessed by the German Version of the Hospital-Anxiety-and-Depression-Scale (HADS, [17]). It comprises 2 subscales (anxiety: HADS-A, depression: HADS-D) with 7 items each. Subscale-scores are interpreted as following:<7 = normal range, 8–10 = borderline, ≥11 = probable presence of a clinical relevant depressive and/or anxiety disorder [18]. The HADS is a widely established instrument to screen for

Table 1
Participants' characteristics (before admission to the epilepsy center, T1).

Gender	Female	50.0% (n = 99)
Age (years, n = 196)	Mean ± SD, median	38.6 ± 14.9, 37.5
	Range	16–75
Status of employment [#]	Employed [a]	41.9% (n = 83)
	Unemployed	15.7% (n = 31)
	Retirement or disability pension	22.7% (n = 45)
	Other (e.g. homekeeper)	17.2% (n = 34)
Age at epilepsy onset (years, n = 193)	Mean ± SD, median	20.3 ± 16.0, 16.0
Duration of epilepsy (years, n = 188)	Mean ± SD, median	17.4 ± 14.8, 13.0
Time since last seizure (months, n = 171)	Mean ± SD, median	4.5 ± 13.2, 1.0
Seizure frequency (in the past six months)[#]	≥1 seizure per day	6.6% (n = 13)
	≥ 1 seizure per week	24.7% (n = 49)
	1–2 seizures per month	19.7% (n = 39)
	3–5 seizures in the last 6 months	18.2% (n = 36)
	1–2 seizures in the last 6 months	16.7% (n = 33)
	No seizures	6.6% (n = 13)
Antiepileptic drugs[#]	None	5.1% (n = 10)
	Monotherapy	23.2% (n = 46)
	Polytherapy	68.2% (n = 135)

SD, standard deviation.
[a] Including occupations in sheltered workshops.
[#] May not sum to 100% due to some missing values.