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Affective and behavioral dysfunction under antiepileptic drugs in epilepsy: Development of a new drug-sensitive screening tool

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ABSTRACT

Objective: Behavioral problems and psychiatric symptoms are common in patients with epilepsy and have a multifactorial origin, including adverse effects of antiepileptic drugs (AEDs). In order to develop a screening tool for behavioral AED effects, the aim of this study was to identify behavioral problems and symptoms particularly sensitive to AED drug load and the presence/absence of AEDs with known negative psychotropic profiles.
Methods: Four hundred ninety-four patients with epilepsy were evaluated who had been assessed with three self-report questionnaires on mood, personality, and behavior (Beck Depression Inventory, BDI; Neurological Disorders Depression Inventory for Epilepsy extended, NDDI-E; and Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen, FPZ). Drug-sensitive items were determined via correlation analyses and entered into an exploratory factor analysis for scale construction. The resulting scales were then analyzed as a function of drug treatment.
Results: Analyses revealed 30 items, which could be allocated to six behavioral domains: *Emotional Lability*, *Depression*, *Aggression/Irritability*, *Psychosis & Suicidality*, *Risk- & Sensation-seeking*, and *Somatization*. Subsequent analysis showed significant effects of the number of AEDs on behavior, as in Emotional Lability ($F = 2.54$, $p = .029$), Aggression/Irritability ($F = 2.29$, $p = .046$), Psychosis & Suicidality ($F = 2.98$, $p = .012$), and Somatization ($F = 2.39$, $p = .038$). Affective and behavioral difficulties were more prominent in those patients taking AEDs with supposedly negative psychotropic profiles. These effects were largely domain-unspecific and primarily manifested in polytherapy.
Conclusion: Drug-sensitive behavioral domains and items were identified which qualify for a self-report screening tool. The tool indicates impairments with a higher drug load and when administering AEDs with negative psychotropic profiles. The next steps require normalization in healthy subjects and the clinical validation of the newly developed screening tool *PsyTrack* along with antiepileptic drug treatment.

1. Introduction

Behavioral and mental problems, such as depression, psychosis, anxiety, and personality disorders, are significantly increased in patients with epilepsy compared with the general population [1]. They represent one of the strongest predictors of self-reported poor quality of life and subjective health status [1–4] while they are often underdiagnosed and undertreated [5]. The lifetime prevalence of psychiatric disorders comorbid to epilepsy ranges from 24 to 52%, underlining the urgent need for a better understanding of their underpinnings [2].

Research strongly supports a multifactorial etiological model of mood and behavioral dysfunction in epilepsy [6] in that (1) epilepsy-related factors such as brain lesions and seizures as well as interictal and periictal epileptic activity and the possibility of shared, bidirectional disease mechanisms; (2) reactive mood and behavioral disturbances due to disease burden, poor adjustment, and lack of social support; and (3) psychotropic side effects of antiepileptic drugs (AEDs) need to be taken into account [4,6–9].

Most AEDs exert their anticonvulsant effects by blocking voltage-gated Na^+ channels and/or Ca^{2+} channels, by enhancing γ-aminobutyric acid (GABA), and/or by inhibiting glutamate transmission. Subsequently, this leads to downstream modulation of the monoaminergic system [10]. Accordingly, AEDs can have positive or negative psychotropic effects depending on the respective compound and mechanisms of action, the underlying neurological condition, and individual patient factors (e.g., history of psychiatric disorders) [6,10–13]. This has important implications for the (risk) management of psychiatric comorbidities in patients with epilepsy under AED treatment [10–12].

However, behavioral and affective functioning is affected not only by the presence or absence of specific AEDs but also the overall drug load, i.e., the number of AEDs [6]. Recently, Witt, Elger, and Helmstaedter demonstrated the negative effects of increasing total drug load on cognition, quantified in two ways: (1) as the number of concurrent AEDs and (2) as the cumulative defined daily dose (DDD) provided by the World Health Organization (WHO; https://www.whocc.no/atc_ddd_index/)

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[14]. They found poorer executive functions with each additional drug given in polytherapy [14].

Therefore, the question arises as to whether the total drug load may also have a similar impact on mood, affect, and behavior, particularly when the therapy includes AEDs with assumedly negative psychotropic profiles. This would put patients with epilepsy undergoing polytherapy at a particular risk for the development of psychiatric disorders. Consequently, close monitoring of mood, affect, and behavior is essential, especially when adapting antiepileptic medication and increasing the total drug load. This requires the availability of a valid screening tool that is not too time-consuming, easily applied and applicable for repeated use. Unfortunately, when monitoring AED side effects, the psychotropic effects of AEDs on mood and behavior are often neglected. Self-rating scales on adverse AED effects, e.g., the Aldenkamp and Baker Neuropsychological Assessment Scale (ABNAS) [15], the Adverse Event Profile (AEP) [16], the Portland Neurotoxicity Scale (PNS) [17], or the Side Effect and Life Satisfaction Scale (SEALS) [18,19], are mostly conceptualized covering physical, physiological, and behavioral domains in a broader, rather superficial way (e.g., the AEP, PNS). Commonly, item collections for such inventories are based on theoretical considerations and clinical experience. Up to now, there is no screening tool available that is explicitly designed and sensitive for assessing AED and drug load-associated behavioral side effects. However, considering the immense use of AEDs in polytherapy and their potential affective and behavioral side effects, availability of such a tool is of utmost importance in clinical practice.

The current study aimed to develop such an AED-sensitive screening tool (*PsyTrack*) by using an empirical–correlational approach for item selection and scale construction, analogous to the construction of the EpiTrack® for cognition [20].

2. Methods

2.1. Patients

The explorative study was based on a sample of patients with epilepsy recruited retrospectively from a fully anonymized clinical database of the Department of Epileptology at the University of Bonn Medical Center. All included patients had undergone an assessment of their behavior, affect/depressive symptomatology, and personality using self-report questionnaires in the period from January 2016 to August 2017. Inclusion criteria were a diagnosis of epilepsy according to the guidelines of the German Neurological Society (DGN), a chronological age of at least 16 years, and being the first assessment of the respective participant in that period, resulting in a total of 494 participants for the study.

2.2. Psychological measures

Within the frame of the behavioral assessment, administered self-report questionnaires were German versions of the Beck Depression Inventory (BDI-I), an extended version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and the Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen (FPZ), a clinical personality scale for neurological populations.

The BDI-I is a reliable and valid 21-item self-rating questionnaire for the assessment of depressive symptoms [21]. Participants rate their mood and behavior (e.g., sadness, feelings of guilt, disappointment, crying) according to four severity ratings per item (0–3). The total score determines the severity of depression, differentiating between absent (0–9), mild (10–18), moderate (19–29), and severe (≥30) depression.

The NDDI-E is a 6-item screening instrument, explicitly developed for the identification of symptoms of depression not overlapping with commonly observed cognitive and adverse effects of AEDs [22]. All items are rated on a 4-tiered scale [4: always or often, 3: sometimes, 2: rarely, and 1: never], with a total score above 15 indicating a clinically relevant depressive symptomatology. Participants rated their symptoms on an adapted version of the NDDI-E, extended by four items to cover further aspects of insecurity ("Ich bin verunsichert/I am insecure"), irritability ("Ich bin gereizt und fahre schnell aus der Haut/I am irritable and easily lose my temper"), delusion ("Ich fühle mich verfolgt, beobachtet, bedroht/I feel persecuted, watched, threatened"), and anxiety ("Ich habe Angst/I am afraid").

The FPZ is a self-rating questionnaire consisting of 98 items assessing frequencies of behaviors in 14 clinically relevant domains: *Mood*, *Emotional Lability*, *Aggression*, *Addiction*, *Anxiety*, *Obsession*, *Drive*, *Reward Learning*, *Self-Determination*, *Impulse Control*, *Novelty/Sensation-Seeking*, *Vegetative Symptoms/Somatization*, *Interpersonal Communication*, and *Perception/Reality Control*. Factor analyses revealed 22 factors (i.e., subscales) as well as four superordinate scales: *Extraversion/Introversion*, *Neuroticism*, *Organic Psychosyndrome* and *Addiction* [6,23]. The FPZ was originally developed for the assessment of behavior and personality in patients with central nervous system diseases, epilepsy in particular. Impaired behaviors are classified as scores 1 SD above or below the mean of the nonclinical norm population in a certain domain. The established factor structure by Helmstaedter and colleagues was confirmed by a validation study [23,24].

2.3. AEDs

The total antiepileptic drug load was quantified in two ways: (1) number of AEDs and (2) total drug load according to the defined daily dose (DDD) provided by the WHO.

Based on review studies [10–12,25] and the package leaflets classifying adverse drug reactions into very common (>1/10), common (≥1/100, up to 1 in 10), uncommon (≥1/1000, up to 1 in 100), rare (≥1/10000, up to 1 in 1000), and very rare (<1/10000), we classified the AEDs into those with negative psychotropic effects in terms of depression, anxiety, and irritability/aggression. An overview of those AEDs with adverse psychotropic side effect profiles is given in Table 1, together with their primary mechanisms of action.

2.4. Statistical analysis

Data analysis was carried out using the statistical software program IBM SPSS Statistics for Windows (version 21.0, Armonk, NY). Frequency and descriptive analyses were conducted for demographics, AED drug load, specific AEDs, epilepsy-related variables, and scores on the administered questionnaires (BDI-I, NDDI-E, and FPZ). In order to overcome different scorings of the questionnaires, all item scores were standardized and transformed into standard values ($M = 100$, $SD = 10$). Antiepileptic drug-sensitive items were extracted by correlation and inference statistics. Item–item correlations were analyzed by principal component analysis (PCA) with a varimax rotation using Kaiser's criterion ($\lambda > 1$). Scale scores, based on the identified factors, were calculated for all participants by averaging the standard values ($M = 100$, $SD = 10$) of the respective items. Differences on these scale scores as a function of number of AEDs and of the presence/absence of drugs with different psychotropic effects (depression, psychosis, anxiety, aggression/irritability) in mono- or polytherapy were analyzed with analyses of variance (ANOVA). Prior to all statistical tests, data were investigated in terms of statistical assumptions for PCA (Kaiser–Meyer–Olkin test and Bartlett's test of sphericity), which were met, and for ANOVA, which were largely met with few exceptions (Levene's test revealed heteroscedasticity for the *PsyTrack* scales Emotional Lability and Psychosis & Suicidality, while scores on the Depression, Psychosis & Suicidality, and Risk- & Sensation-seeking scales showed some violation of normality).

3. Results

The evaluated patient group consisted of 494 patients (51.2% female) with an age range of 16 to 87 years ($M = 40.91$, $SD = 15.88$).