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Effect of long-term administration of clonazepam, carbamazepine, and valproate on cognitive, psychological, and personality changes in adult epilepsy: a case–control study

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Abstract

Background: Epilepsy can be treated with antiepileptic drugs (AEDs) which may have psychiatric and behavioral side effects. Additionally, the availability of new AEDs has increased, and our understanding of variability to combinations of several AEDs has evolved. Based on the treatment outcomes of carbamazepine, valproate, and clonazepam, this study aims to compare the cognitive function, personality, and psychological issues associated with these drugs and evaluate seizure-related factors related to them. Only 139 participants were included. Clonazepam was used as an add-on antiepileptic drug. Participants were categorized into five groups: group 1, carbamazepine; group 2, valproate; group 3, carbamazepine and clonazepam; group 4, valproate and clonazepam; and group 5, epileptic patients without AED. All participants were assessed using the Wechsler Adult Intelligence Scale (WAIS), Structured Interview for the Five-Factor Personality Model (SIFFM), Hamilton Anxiety and Depression Rating Scale, and Minnesota Multiphasic Personality Inventory-2 (MMPI-2).

Results: In the WAIS, group 1 had the worst mean of verbal intelligence quotient (*IQ*). Moreover, group 3 was more vulnerable in symptomatic response in all subscales of MMPI-2 except the masculinity–femininity subscale and a high percentage in moderate severity of anxiety and depression in the Hamilton scales.

Conclusions: The use of clonazepam and carbamazepine might increase the incidence of behavioral problems especially increased severity of anxiety and depression and decreased performance *IQ* compared with either clonazepam or carbamazepine alone. Moreover, patients with carbamazepine treatment might have more personality changes and lowered verbal *IQ* than others.

Keywords: Clonazepam, Intelligence, Personality, Epilepsy, Valproate, Carbamazepine

Background

Epilepsy is a chronic neurodevelopmental disorder significantly associated with cognitive and neuropsychiatric comorbidities, adversely affecting epileptic patients' life [1]. Antiepileptic drugs (AEDs) are used to control epilepsy. Both epilepsy and using AED in patients have prevalent cognitive impairments and psychiatric and behavioral side effects (PBSE). Both mild behavioral modifications to severe depression and even suicide can include these effects [2].

Cognitive impairments in epilepsy result from complex interactions between etiology, seizures, interictal discharges, and AED [3]. To date, there is no specific treatment for these patients' cognitive impairment [4]. Meanwhile, the potential effect for all AED to have the negative side is that it slows down cognition. This is due to the drug's nature that inhibits brain "over-activity."

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Some symptoms can improve with time; for example, 72% of patients treated with clobazam showed improvement in cognition [5]. Also, some AED had minimal cognitive side effects as valproic acid. The cognitive side effects of AEDs generally decrease after dose reduction or discontinuation [6].

Individuals with epilepsy have a high prevalence of psychiatric comorbidity. A previous study for 1058 epileptic patients reported that epileptic people are associated with psychiatric comorbidity, and men have a common complaint of aggression, depression, irritability, anxiety, and mood instability. In contrast, women and patients with focal-onset seizures commonly have psychiatric diagnoses. Moreover, patients with generalized seizures and patients receiving sodium channel-blocking AEDs are less common have psychiatric problems [7]. In addition, AED treatment can negatively affect mood and behavior and further complicate the situation [2]. It is believed that as many as 30% of newly diagnosed patients and 50% of those with drug-resistant epilepsy are affected [8]. Depression, anxiety disorders, and psychosis are especially common [9]. Thus, it is challenging to recommend AED treatment especially to patients with psychiatric symptoms [10].

Epilepsy patients also display personality traits, such as low self-directedness, the high pursuit of novelty, avoidance of harm, and impulsiveness [11]. In epileptic patients, a relationship had been observed between the changes of personality and behavioral problems as neurotics have been strongly consistent with widespread evidence showing that it is a risk factor in developing depression in the general population [12]. The effect of AED on personality changes is still unclear.

Additionally, the availability of new AEDs has increased, and our understanding of variability between patients or within the same patient treated with one AED, or combinations of several AEDs, has evolved [13]. So, the AED effect on comorbid conditions needs to be investigated. Moreover, it is clinically important and useful to obtain information about the incidence rate of PBSE in patients treated with AED to choose the appropriate AED treatment method [14].

Benzodiazepines (BDZ) are frequently employed in the management of epilepsy, using their properties as central nervous system (CNS) depressants to reduce seizure activity or as an adjunctive medication to avoid seizures. Clobazam and clonazepam are good choices for seizure control in people with epilepsy that are refractory to various antiepileptic medications. Because of its affinity with the GABA-A receptor alpha-2 subunit, clonazepam is the most used benzodiazepine for the long-term treatment of epilepsy [15]. However, clonazepam is usually used to add to other antiepileptic drugs that consider a challenge for studying its long effect on epileptic patients. We aimed to study carbamazepine and valproic acid as previously studied in many research studies and compare them with long-term clonazepam as add-on therapy. Therefore, based on the treatment outcomes of carbamazepine, valproate, and clonazepam, this study aimed to compare the cognitive function, personality, and psychological issues associated with these antiepileptic drugs as well as to evaluate seizure-related factors associated with them.

Methods

Participants and procedures

This is a cross-sectional case–control study. All participants included 139 patients admitted from March 2021 to June 2021 at the Assiut University Hospital adult outpatient epilepsy clinic. The following inclusion criteria are fulfilled for all enrolled patients: (1) age between 18 and 50 years and (2) matching the clinical, imaging, and electroencephalographic (EEG) diagnosis symptoms of idiopathic epilepsy.

In our epilepsy clinic, clonazepam is a good choice for seizure control in people with epilepsy that are refractory to various antiepileptic medications and is mostly used as add-on medication to the other AED. Through the indirect method, we studied clonazepam and evaluated its clinical efficacy compared to carbamazepine and valproate alone. In this research, 99 epileptic patients with AED and 40 epileptic patients without AED (new diagnosis with epilepsy) were assigned as the control group. So, the participants were classified into different groups based on the drugs administered: group 1, carbamazepine; group 2, valproate; group 3, carbamazepine and clonazepam; group 4, valproate and clonazepam; and group 5, epileptic patients without AED.

Measure

After written informed consent was obtained from the participants, the studied samples had the following.

A detailed interview with personal demographic data

A detailed interview with personal demographic data, such as age, sex, education, history of occupation, past medical history, family history, and medical, neurological, and psychiatric disorders, was conducted.

Information on the clinical features of epilepsy

Information on the clinical features of epilepsy, including the duration of epilepsy, the duration of drug intake, the frequency of seizures, the type of seizure, and the use of AED, was collected from all participants. Neuroimaging findings were obtained and analyzed to confirm the absence of structural changes.

Intelligence assessment using the Arabic version of the Wechsler Adult Intelligence Scale (WAIS)

The test consists of six verbal subtests and five performance subtests. All of the samples studied were obtained in accordance with the Deterioration Index. In each subtest, we calculated the score and got the quotient of verbal intelligence (*VIQ*), performance intelligence quotient, and full intelligence quotient. Cognitive function was assessed at least 1 week after the last attack in epileptic patients to avoid interference from transient cognitive impairment after seizures.

Conventional EEG study

Eight-channel standard wakefulness EEG was conducted using the Nihon Kohden system model (4217). With hyperventilation and photostimulation for each patient, monopolar, bipolar, and double-distance montages were performed. In terms of background activity and the presence of any epileptogenic activity, EEG tracings were carefully analyzed.

The Structured Interview for the Five-Factor Personality Model (SIFFM) [16]

The Five-Factor Personality Model is a model based on general language personality descriptors, and its theory suggests five broad dimensions that are commonly used to describe human personality [11, 12]. The five factors defined by the acronyms OCEAN or CANOE were openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism.

Assessment of the Hamilton Depression Rating Scale [17]

It is a clinical rating scale for assessing depression severity. The total score is obtained by summing each item's score (0–4) (symptom is absent, mild, moderate, or severe). Scores can range from 0 to 54 for the 17-item version. Moreover, total scores of 0 to 7 do not indicate depression, scores of 8 to 13 indicate mild depression, scores of 14 to 18 indicate moderate depression, scores of 19 to 22 indicate severe depression, and scores of 23 or more indicate very severe depression.

The Hamilton Anxiety Rating Scale [18]

The Hamilton Anxiety Rating Scale [18] is a clinician-rated scale intended to analyze the severity of anxiety. The scale consists of 14 items. Each item is scored on a scale from 0 (not present) to 4 (severe), with a total score range of 0–56, wherein the overall score is 0–13 = normal, 14–17 = mild anxiety, 18–24 = moderate anxiety, and 25–30 = severe anxiety.

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) [19]

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) [19] is a psychological test with a range of symptoms of psychopathology and personality traits that are maladaptive. It is designed with 10 clinical scales that evaluate 10 major categories of abnormal human behavior and four validity scales that assess the test's accuracy. The clinical scales include the following: 1, hypochondriasis (Hs); 2, depression (D); 3, hysteria (Hy); 4, psychopathic deviation (Pd); 5, masculinity–femininity (Mf); 6, paranoia (Pa); 7, psychophrenia (Pt); 8, schizophrenia (Sc); 9, hypomania (Ma); and 10, social introversion (Si). According to the *T*-score, more than 65 responses were considered symptomatic in each clinical subscale, 45–65 borderline, and less than 45 normal.

Statistical analysis

Data were gathered and analyzed using Statistical Package for the Social Science (SPSS, version 26). Continuous data were expressed as mean ± standard error, whereas nominal data were expressed as frequency (percentage). In this study, the chi-square test was used to compare nominal data, whereas the Kruskal-Wallis test was used to compare continuous data from different groups. The correlation model was done by Spearman coefficients. The confidence level was maintained at 95%, and the *P* value was considered significant if it was < 0.05.

Results

Demographic data

In this study, 139 participants had been recruited: 99 epileptic patients with AED and 40 epileptic patients without AED. Of the 99 epileptic patients, four groups were classified by type of antiepileptic medication. A statistically significant difference regarding age, sex, marital status, and education was observed (P <0.05), as shown in Table 1. Group 1 has the highest mean age (41.86 ± 12.56), whereas group 2 has the lowest mean age (27.83 ± 6.32). Males were more prominent in all groups, except group 1 (28.6%) and group 4 (40%). Most of the participants were illiterate, except for group 2, who had a high percentage of high educational levels (66.7%) relative to illiterate level. All studied groups had a high percentage of being married and not working except group 2.

Clinical features of epilepsy among participants

Significant statistical differences in seizure frequency, type of seizure, and EEG changes (P < 0.001) are shown in Table 2. Most participants had seizures less than six

Table 1 Demographic data of studied groups

Variables	Group 1 *N* = 35 *N* (%)	Group 2 *N*=18 *N* (%)	Group 3 *N* = 31 *N* (%)	Group 4 *N* = 15 *N* (%)	Group 5 *N* = 40 *N* (%)	*P* value
Age (mean ±SE)	41.86 ± 12.56	27.83 ± 6.32	37.35 ± 8.63	34.80 ± 12.63	36.13 ± 11.13	0.002*
Sex						
Male	10 (28.6%)	15 (83.3%)	21 (67.7%)	6 (40%)	31 (51.5%)	0.001*
Female	25 (71.4%)	3 (16.7%)	10 (32.3%)	9 (60%)	29 (48.3%)	
Marital status						
Single	8 (22.9%)	9 (50%)	11 (35.5%)	3 (20%)	20 (33.3%)	0.03*
Married	25 (71.4%)	9 (50%)	18 (58%)	9 (60%)	38 (63.3%)	
Divorce	0 (0%)	0 (0%)	2 (6.5%)	0 (0%)	0 (0%)	
Widow	2 (5.7%)	0 (0%)	0 (0%)	3 (20%)	2 (3.3%)	
Education						
Illiterate	32 (91.4%)	6 (33.3%)	25 (80.6%)	9 (60%)	33 (55%)	0.000*
Primary education	0 (0%)	0 (0%)	3 (9.7%)	0 (0%)	10 (16.7%)	
High education	3 (8.6%)	12 (66.7%)	3 (9.7%)	6 (40%)	17 (28.3%)	
Occupation state						
Not working	28 (80%)	9 (50%)	17 (54.8%)	9 (60%)	33 (55%)	0.172
Employers	7 (20%)	9 (50%)	14 (45.2%)	6 (40%)	27 (45%)	

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value

Table 2 Clinical features of epilepsy among participants

Variables	Group 1 *N* = 35 *N* (%)	Group 2 *N* = 18 *N* (%)	Group 3 *N* = 31 *N* (%)	Group 4 *N* = 15 *N* (%)	Group 5 *N* = 40 *N* (%)	*P* value
Frequency of seizures						
Less than 6 times\month	35 (100%)	15 (83.3%)	28 (90.3%)	9 (60%)	32 (80%)	0.000*
More than 6 times\month	0 (0%)	3 (16.7%)	3 (9.7%)	6 (40%)	8 (20%)	
Type of seizures						
Generalized	0 (0%)	18 (100%)	20 (70.9%)	15 (100%)	21 (52.5%)	0.000*
Partial	35 (100%)	0 (0%)	5 (16.1%)	0 (0%)	19 (47.5%)	
Absence	0 (0%)	0 (0%)	2 (6.5%)	0 (0%)	0 (0%)	
Myoclonus	0 (0%)	0 (0%)	2 (6.5%)	0 (0%)	0 (0%)	
Duration of illness						
Less than 5 years	11 (31.4%)	1 (5.6%)	11 (35.5%)	0 (0%)	40 (100%)	0.001*
5–10 years	18 (51.4%)	5 (27.8%)	10 (32.3%)	12 (80%)	0 (0%)	
More than 10 years	6 (17.1%)	12 (66.7%)	10 (32.3%)	3 (20%)	0 (0%)	
EEG changes						
Non-specific changes	27 (77.2%)	8 (44.4%)	19 (61.3%)	12 (80%)	14 (35%)	0.0003*
Generalized	0 (0%)	10 (55.6%)	3 (9.7%)	3 (20%)	15 (37.5)	
Focal	8 (22.8%)	0 (0%)	9 (29%)	0 (0%)	11 (27.5%)	
1. Temporal site	6 (17.1%)	0 (0%)	7 (22.5%)	0 (0%)	7 (17.5%)	
2. Frontal site	2 (5.7%)	0 (0%)	2 (6.5%)	0 (0%)	4 (10%)	

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value

times per month, with disease duration and 5–10 years of drug intake and non-specific EEG changes. The generalized type was the most prominent in all groups except groups 1 and 3. On the other hand, group 3 presented with myoclonic-absence seizures, whereas group 1 presented with partial seizures.

Table 3 The Wechsler Adult Intelligence Scale among the studied samples

Variables	Group 1 *N* = 35 Mean ± *SE*	Group 2 *N* = 18 Mean ± *SE*	Group 3 *N* = 31 Mean ± *SE*	Group 4 N = 15 Mean ± *SE*	Group 5 *N* = 40 Mean ± *SE*	*P* value
Verbal *IQ*	79.35 ± 0.56	81.5 ± 0.45	80.8 ± 0.8	79.8 ± 0.2	87.3 ± 0.4	0.001*
Performance *IQ*	92.41 ± 0.71	92 ± 0.91	88.96 ± 0.8	91 ± 0.67	94 ± 0.8	0.007*
Total *IQ*	83.02 ± 0.4	84.6 ± 1.4	82.3 ± 0.5	82.2 ±0.106	89.6 ± 0.5	0.108
DI	9.12 ± 1.3	8.9 ± 2.06	9.16 ± 1.24	9.05 ± 2.9	1.16 ± 1.38	0.001*

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value, *DI* Deterioration Index

The Wechsler Adult Intelligence Scale

Table 3 shows that all subscales of WAIS have significant statistical differences ($P < 0.001$) except total *IQ*. Group 5 had the highest mean score among the different groups in all WAIS subscales. Group 1 and group 4 had the lowest mean of verbal *IQ* (79.35 ± 0.56 and 79.8 ± 0.2, respectively), whereas group 3 and group 4 had the lowest mean of performance *IQ* and total *IQ*. It was observed that group 3 had the worst mean score for the Deterioration Index (*DI*) (9.162 ± 1.249), followed by group 1 (9.128 ± 1.3), group 4 (9.05 ± 2.9), and group 2 (8.9 ± 2.06).

The Structured Interview for the Five-Factor Model of Personality (SIFFM)

Significant statistical differences were observed in all subscales of SIFFM, except the agreeableness subscale ($P < 0.05$), as shown in Table 4. In the neuroticism, extraversion, agreeableness, and conscientiousness subscales, all groups demonstrate a significant percentage of intermediate response relative to low and high responses. With regard to neuroticism and agreeableness, the highest percentage of response rates was observed in group 1 and group 3 (11.43% vs. 6.45%) (2.9% vs. 3.2%), respectively. The only group with high response rates in the conscientiousness subscale were

Table 4 The distribution of the Structured Interview for the Five-Factor Model of Personality among the studied samples

Variables	Group 1 *N* = 35 *N* (%)	Group 2 *N* = 18 *N* (%)	Group 3 *N* = 31 *N* (%)	Group 4 *N* = 15 *N* (%)	Group 5 *N* = 40 *N* (%)	*P* value
Neuroticism						
Low	8 (22.86%)	0 (0%)	0 (0 %)	3 (20%)	10 (25%)	0.017*
Intermediate	23 (65.71)	18 (100%)	29 (93.55%)	12 (80%)	28 (70%)	
High	4 (11.43%)	0 (0%)	2 (6.45%)	0 (0%)	2 (5%)	
Extraversion						
Low	9 (25.7%)	0 (0%)	8 (25.8%)	0 (0%)	6 (15%)	0.002*
Intermediate	26 (74.3%)	15 (83.3%)	23 (74.2%)	15 (100%)	27 (67.5%)	
High	0 (0%)	3 (16.7%)	0 (0%)	0 (0%)	7 (17.5%)	
Openness to experience						
Low	26 (74.3%)	9 (50%)	28 (90.3%)	12 (80%)	29 (72.5%)	0.038*
Intermediate	9 (25.7%)	9 (50%)	3 (9.7%)	3 (20%)	11 (27.5%)	
Agreeableness						
Low	2 (5.7%)	0 (0%)	1 (3.2%)	0 (0%)	4 (10%)	0.614
Intermediate	32 (91.4%)	18 (100%)	29 (93.5%)	15 (100%)	36 (90%)	
High	1 (2.9%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	
Conscientiousness						
Low	10 (28.6%)	0 (0%)	12 (38.7%)	0 (0%)	10 (25%)	0.025*
Intermediate	24 (68.6%)	18 (100%)	19 (61.3%)	15 (100%)	30 (75%)	
High	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value

group 1 (2.9%). On the other hand, a high percentage of extraversion response rates has been observed in group 2 and group 5 (16.7% and 17.5%, respectively).

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2)

Table 5 shows all subscales of MMPI-2 have significant statistical differences ($P < 0.001$). In the psychopathic deviate, schizophrenia, and social introversion subscales,

Table 5 The Minnesota Multiphasic Personality Inventory (MMPI-2) among the studied samples

MMPI-2 variables	Group 1 *N* = 35 *N* (%)	Group 2 *N* = 18 *N* (%)	Group 3 *N* = 31 *N* (%)	Group 4 *N* = 15 *N* (%)	Group 5 *N* = 40 *N* (%)	*P* value
Hypochondriasis						
Normal	4 (11.4%)	3 (16.7%)	4 (12.9%)	0 (0%)	14 (35%)	0.000*
Borderline	23 (65.7%)	12 (66.7%)	15 (48.4%)	15 (100%)	26 (65%)	
Symptomatic	8 (22.9%)	3 (16.7%)	12 (38.7%)	0 (0%)	0 (0%)	
Depression						
Normal	14 (40%)	3 (16.7%)	1 (3.2%)	9 (60%)	30 (75%)	0.000*
Borderline	10 (28.6%)	12 (66.7%)	14 (45.2%)	3 (20%)	10 (25%)	
Symptomatic	11 (31.4%)	3 (16.7%)	16 (51.6%)	3 (20%)	0 (0%)	
Conversion hysteria						
Normal	5 (14.3%)	3 (16.7%)	4 (12.9%)	3 (20%)	17 (42.5%)	0.000*
Borderline	21 (60%)	12 (66.7%)	12 (38.7%)	9 (60%)	23 (57.5%)	
Symptomatic	9 (25.7%)	3 (16.7%)	15 (48.4%)	3 (20%)	0 (0%)	
Psychopathic Deviate						
Normal	14 (40%)	9 (50%)	6 (19.4%)	0 (0%)	33 (82.5%)	0.000*
Borderline	20 (57.1%)	9 (50%)	18 (58.1%)	15 (100%)	7 (17.5%)	
Symptomatic	1 (2.9%)	0 (0%)	7 (22.6%)	0 (0%)	0 (0%)	
Masculinity–femininity						
Normal	7 (20%)	12 (66.7%)	8 (25.8%)	0 (0%)	19 (47.5%)	0.000*
Borderline	17 (48.6%)	6 (33.3%)	21 (67.7%)	15 (100%)	12 (30%)	
Symptomatic	11 (31.4%)	0 (0%)	2 (6.5%)	0 (0%)	9 (22.5%)	
Paranoia						
Normal	20 (57.1%)	9 (50%)	9 (29%)	6 (40%)	33 (82.5%)	0.000*
Borderline	14 (40%)	9 (50%)	14 (45.2%)	9 (60%)	6 (15%)	
Symptomatic	1 (2.9%)	0 (0%)	8 (25.8%)	0 (0%)	1 (2.5%)	
Psychasthenia						
Normal	17 (48.6%)	3 (16.7%)	9 (29%)	9 (60%)	33 (82.5%)	0.000*
Borderline	18 (51.4%)	15 (83.3%)	17 (54.8%)	6 (40%)	7 (17.5%)	
Symptomatic	0 (0%)	0 (0%)	5 (16.1%)	0 (0%)	0 (0%)	
Schizophrenia						
Normal	16 (45.7%)	9 (50%)	6 (19.4%)	9 (60%)	34 (85%)	0.000*
Borderline	14 (40%)	9 (50%)	20 (64.5%)	6 (40%)	6 (15%)	
Symptomatic	5 (14.3%)	0 (0%)	5 (16.1%)	0 (0%)	0 (0%)	
Hypomania						
Normal	26 (74.3%)	6 (33.3%)	16 (51.6%)	6 (40%)	32 (80%)	0.000*
Borderline	9 (25.7%)	12 (66.7%)	9 (29%)	9 (60%)	8 (20%)	
Symptomatic	0 (0%)	0 (0%)	6 (19.4%)	0 (0%)	0 (0%)	
Social introversion						
Normal	20 (57.1%)	15 (83.3%)	8 (25.8%)	9 (60%)	36 (90%)	0.000*
Borderline	12 (34.3%)	3 (16.7%)	18 (58.1%)	6 (40%)	4 (10%)	
Symptomatic	3 (8.6%)	0 (0%)	5 (16.1%)	0 (0%)	0 (0%)	

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value

the highest frequency of symptomatic response was observed in group 3 followed by group 1. On the other hand, the significantly highest percentage of symptomatic response in the masculinity–femininity subscale was observed in group 1 (31.4%), followed by group 5 (22.5%) and group 3 (6.5%). The symptomatic response in the hypomania and psychasthenis subscales were only observed in group 3.

Regarding paranoia, group 3 had the highest proportion of symptomatic responses (25.8%), whereas group 5 had the lowest proportion (2.5%). In contrast, group 3 had the highest symptomatic response of hypochondriasis, conversion hysteria, and depression, whereas group 2 had the lowest frequency.

The Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HDRS)

Statistically significant differences were observed between the studied groups based on results of the HAM-A and HDRS ($P < 0.001$) as shown in Table 6. In HAM-A, the highest frequency of mild degree of anxiety was observed in group 3 (22.6%) followed by group 1 (2.9%), whereas the significantly highest frequency of moderate anxiety was observed in group 3 (9.7%) followed by group 1 (2.9%).

Based on the HDRS, the highest frequency of mild degree of depression was observed in group 2 (66.7%), followed by group 4 (60%). In contrast, the highest frequency of moderate degree of depression was observed in group 3 (71%).

Correlation model

There is a weak positive correlation between age and *DI*. Also, the frequency of seizures had a positive correlation with verbal *IQ* and total *IQ* (see Table 7 in supplement file).

Discussion

Epilepsy is a chronic neurodevelopmental disorder and can be treated with AED. It is significantly important to study the likelihood of developing PBSE to improve the efficacy of AED [14] and compare each drug effect to help in choosing the appropriate treatment method. Therefore, we compared the treatment outcomes of carbamazepine, valproate, and clonazepam about cognitive function, personality, and behavioral issues in epilepsy and evaluated the seizure-related factors associated with them.

In this study, we found that all groups demonstrate a significant percentage of intermediate (borderline) response in the neuroticism, extraversion, agreeableness, and conscientiousness subscales, relative to low (normal) and high (abnormal) responses. It was noticed that the carbamazepine group had the highest response in neuroticism (11.43%), agreeableness (2.9%), and conscientiousness (2.9%). In contrast, the carbamazepine and clonazepam group had the highest frequency in symptomatic response in all subscales of MMPI-2 except the masculinity–femininity subscale. Also, based on the Hamilton scales, the carbamazepine and clonazepam group had a high percentage in moderate severity of anxiety and depression.

Carbamazepine (CBZ) is commonly used in the treatment of focal epilepsy [20]. Moreover, dysfunctional personality patterns vary depending on the epileptogenic zone. This may explain the high percentage of personality changes in the carbamazepine group. It was noticed that the presence of depression might trigger the participants to report their premorbid personality erroneously; available evidence supports the consistency in personality reports, including neuroticism [21].

Regarding psychiatric disorders, for decades, the treatment of psychiatric disorders has been based on anticonvulsant medications. The biochemical mechanisms

Table 6 The Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HDRS) among the studied samples

Variables	Group 1 *N* = 35 *N* (%)	Group 2 *N*=18 *N* (%)	Group 3 *N*=31 *N* (%)	Group 4 *N*=15 *N* (%)	Group 5 *N*=40 *N* (%)	*P* value
HAM-A						
Normal	33 (94.3%)	18 (100%)	21 (67.7%)	15 (100%)	40 (100%)	0.001*
Mild	1 (2.9%)	0 (0%)	7 (22.6%)	0 (0%)	0 (0%)	
Moderate	1 (2.9%)	0 (0%)	3 (9.7%)	0 (0%)	0 (0%)	
HDRS						
Normal	16 (45.7%)	3 (16.7%)	5 (16.1%)	3 (20%)	26 (65%)	0.000*
Mild	11 (31.4%)	12 (66.7%)	4 (12.9%)	9 (60%)	14 (35%)	
Moderate	8 (22.9%)	3 (16.7%)	22 (71.0%)	3 (20%)	0 (0%)	

Group 1: carbamazepine, group 2: valproate, group 3: carbamazepine and clonazepam, group 4: valproate and clonazepam, group 5: epileptic patients without antiepileptic drugs (AEDs), *significant *P* value

behind their antiseizure activity can also lead to mood and behavior stabilization [22]. As a mood stabilizer in acute mania and/or as a maintenance treatment of bipolar disorder in adults, valproate and carbamazepine are proven to be effective in preventing recurrence [23]. In contrast, the incidence of PBSE can increase with the increase in the dose of AED [24]. Further research is needed on the relation between AED action mechanisms and psychiatric symptoms which involves numerous cortical and subcortical brain systems; brain areas, such as the hippocampus; and ion channel and neurotransmitter systems, including monoamines, glutamates, and gamma-aminobutyric acid [9]. Previous studies considered psychological variables (stressful life events, ancient history of depression, neuroticism, social support) [25]. Another previous study has shown a high stigma prevalence and a subsequent risk of depression especially in epileptic patients (refractory epilepsy, mesial temporal sclerosis, or postsurgical PWE) [26].

In this study, based on the WAIS, the carbamazepine group had the worst mean of verbal *IQ*, whereas the valproate group had the worst mean of performance *IQ*. Valproate and clonazepam had the worst mean of *DI* index and the second worst mean of performance *IQ* and total *IQ*.

Carbamazepine was subsequently associated with verbal episodic memory deficits in newly diagnosed epilepsy patients [27]. However, in patients and volunteers, the most clinically important cognitive effect of carbamazepine may impair executive function, including speed and attention to information processing [28]. On the other hand, the previous study has demonstrated that valproate has minor adverse effects on cognitive function [29]. Also, it was reported that impaired motor skills improved after the discontinuation of valproate in a double-blind, placebo-controlled study [30].

In contrast, significant difficulties were found for long-term benzodiazepine users in the areas of working memory, processing speed, divided attention, vasoconstriction, recent memory, and expressive language [31]. This indicates that benzodiazepine acts as a GABA-A receptor agonist. The GABA-A, an inhibitory neurotransmitter, may impact cognitive performance [32]. Yet, because of the distribution of GABA-A receptors across the CNS (e.g., cerebral cortex), benzodiazepines can cause certain adverse effects if chronically used [33]. Deleterious cognitive functions of benzodiazepines, such as anterograde and retrograde amnesia, are likely to occur due to GABAergic activation [34]. Another key system thought to be affected by benzodiazepines is the cholinergic system. The cholinergic system, which is made of several structures in the CNS, is involved in memory storage and recovery as well as arousal in addition to attention and perception. Research shows that the cholinergic system most commonly involves cognitive skills like learning, memory, attention, and executive function, along with histamine, GABA, and opioid receptor paths [32].

In this study, more than half of the participants had a duration of illness from 5 to 10 years, frequency of seizure less than 6 times per month, and non-specific changes in EEG. In contrast, the majority of the participants had a generalized type of seizure. In addition, there is a weak positive correlation between age and *DI*. Also, the frequency of seizures had a positive correlation with verbal *IQ* and total *IQ*.

Regarding epilepsy-related variables, a systematic study for the relationship between psychiatric comorbidity and epilepsy-related variables reported a link between depression only with seizure frequencies [35]. In contrast, a previous study proposed that generalized tonic-clonic, myoclonic, and partial seizures could also be important risk factors for depression [36]. In addition, depression has induced stress and anxiety, seizure recurrence, and seizure frequency changes [37].

Although the current study has significant results, some limitations exist. This study not only should rely on measures of *IQ* but should also include the evaluation of all other cognitive domains. Several researches were done by using different psychometric tests to evaluate cognitive and psychiatric manifestation without providing normative data for patients with epilepsy to help in the diagnosis and treatment of those patients. Another limitation in this study is the small size number.

Conclusions

Overall, the results of this study found a link between AED and cognitive and behavioral changes in epileptic patients. These findings indicate the importance of screening for cognitive and behavioral changes in epileptic patients especially those treated by more than one antiepileptic drug. The use of clonazepam with carbamazepine might increase the incidence of behavioral problems, increase the severity of anxiety and depression, and decrease performance *IQ* compared with using either clonazepam or carbamazepine alone. Furthermore, patients with carbamazepine treatment might have more personality changes and lowered verbal *IQ* than any other studied drug.

Abbreviations

AED: Antiepileptic drug; PBSE: Psychiatric and behavioral side effects; WAIS: Wechsler Adult Intelligence Scale; SIFFM: Structured Interview for the Five-Factor Personality Model; HAM-A: Hamilton Anxiety Rating Scale; MMPI-2: Minnesota Multiphasic Personality Inventory-2.

Supplementary Information

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Additional file 1: Table 7. correlation between age, frequency of seizures, duration of disease and all subscales of the Wechsler adult intelligence scale.

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GA and SM recruited participants, analyzed and interpreted the data, and were the contributors in writing the manuscript. KE and YE revised data interpretation and read and approved the final manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
The study received ethical approval from Assiut University, Faculty of Medicine'sinstitutional review board (IRB). This research was registered on the clinical trial (NCT04792658) on 11 March 2021, EUL: https://www.clinicaltrials.gov/ct2/show/NCT04792658. All participants had written informed consent to take part in the research. They were assured of data protection and were informed that data in anonymized form would be available. This study was carried out in accordance with the latest version of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. LaRoche SM, Helmers SL (2004) The new antiepileptic drugs: clinical applications. Jama. 291(5):615–620. https://doi.org/10.1001/jama.291.5.615
2. Piedad J, Rickards H, Besag FMC, Cavanna AE (2012) Beneficial and adverse psychotropic effects of antiepileptic drugs in patients with epilepsy. CNS Drugs 26(4):319–335. https://doi.org/10.2165/11599780-000000000-00000
3. Raspall-Chaure M, Neville BG, Scott RC (2008) The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol 7(1):57–69. https://doi.org/10.1016/S1474-4422(07)70324-1
4. Mosaku KS, Fatoye FO, Komolafe M, Lawal M, Ola BA (2006) Quality of life and associated factors among adults with epilepsy in Nigeria. Int J Psychiatry Med 36(4):469–481. https://doi.org/10.2190/R80G-580X-X1H2-6936
5. Eddy CM, Rickards HE, Cavanna AE (2011) The cognitive impact of antiepileptic drugs. Ther Adv Neurol Disord 4(6):385–407. https://doi.org/10.1177/1756285611417920
6. Witt JA, Helmstaedter C (2013) Monitoring the cognitive effects of antiepileptic pharmacotherapy--approaching the individual patient. Epilepsy Behav 26(3):450–456. https://doi.org/10.1016/j.yebeh.2012.09.015
7. Stephen LJ, Wishart A, Brodie MJ (2017) Psychiatric side effects and antiepileptic drugs: observations from prospective audits. Epilepsy Behav 71(Pt A):73–78. https://doi.org/10.1016/j.yebeh.2017.04.003
8. Lin JJ, Mula M, Hermann BP (2012) Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 380(9848):1180–1192. https://doi.org/10.1016/S0140-6736(12)61455-X
9. Brandt C, Mula M (2016) Anxiety disorders in people with epilepsy. Epilepsy Behav 59:87–91. https://doi.org/10.1016/j.yebeh.2016.03.020
10. Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S et al (2016) Epilepsy, antiepileptic drugs, and aggression: an evidence-based review. Pharmacol Rev 68(3):563. https://doi.org/10.1124/pr.115.012021
11. Yazici E, Yazici AB, Aydin N, Orhan A, Kirpinar I, Acemoglu H (2013) Temperament and character traits in patients with epilepsy: epileptic personality. J Nerv Ment Dis 201(5):365–370. https://doi.org/10.1097/NMD.0b013e31828e0e3d
12. Kendler KS, Gatz M, Gardner CO, Pedersen NL (2006) Personality and major depression: a Swedish longitudinal, population-based twin study. Arch Gen Psychiatry 63(10):1113–1120. https://doi.org/10.1001/archpsyc.63.10.1113
13. Landmark CJ, Johannessen SI, Tomson T (2016) Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. Epileptic Disorders 18(4):367–383. https://doi.org/10.1684/epd.2016.0880
14. Chen B, Choi H, Hirsch LJ, Legge A, Buchsbaum R, Detyniecki K (2018) Cross-sensitivity of psychiatric and behavioral side effects with antiepileptic drug use. Seizure. 62:38–42. https://doi.org/10.1016/j.seizure.2018.09.014
15. Ochoa JG, Kilgo WA (2016) The role of benzodiazepines in the treatment of epilepsy. Curr Treat Options Neurol 18(4):18. https://doi.org/10.1007/s11940-016-0401-x
16. Trull TJ, Widiger TA. Structured interview for the five-factor model of personality (SIFFM): Professional manual. Psychological Assessment Resources, Incorporated; 1997.
17. Hamilton M, Guy W (1976) Hamilton depression scale. Group. 1:4
18. Hamilton M (1959) Hamilton anxiety scale. Group. 1:4
19. Butcher JN, Graham JR, Williams CL, Ben-Porath YS (1990) Development and use of the MMPI-2 Content Scales. Development and use of the MMPI-2 Content Scales. University of Minnesota Press, Minneapolis, MN, US
20. Liguori C, Izzi F, Manfredi N, Mercuri NB, Placidi F (2018) Lacosamide may improve cognition in patients with focal epilepsy: EpiTrack to compare cognitive side effects of lacosamide and carbamazepine. Epilepsy Behav Case Rep 10:35–37. https://doi.org/10.1016/j.ebcr.2018.02.004
21. Novais F, Franco A, Loureiro S, Andrea M, Figueira ML, Pimentel J et al (2019) Personality patterns of people with medically refractory epilepsy - does the epileptogenic zone matter? Epilepsy Behav 97:130–134. https://doi.org/10.1016/j.yebeh.2019.05.049
22. Gobbi G, Janiri L (2006) Sodium- and magnesium-valproate in vivo modulate glutamatergic and GABAergic synapses in the medial prefrontal cortex. Psychopharmacology. 185(2):255–262. https://doi.org/10.1007/s00213-006-0317-3
23. Findling RL, Chang K, Robb A, Foster VJ, Horrigan J, Krishen A et al (2015) Adjunctive maintenance lamotrigine for pediatric bipolar I disorder: a placebo-controlled, randomized withdrawal study. J Am Acad Child Adolesc Psychiatry 54(12):1020–1031. e3. https://doi.org/10.1016/j.jaac.2015.09.017
24. Bortz JJ (2003) Neuropsychiatric and memory issues in epilepsy. Mayo Clin Proc 78(6):781–787. https://doi.org/10.4065/78.6.781
25. Lee SA, Lee SM, No YJ (2010) Factors contributing to depression in patients with epilepsy. Epilepsia. 51(7):1305–1308. https://doi.org/10.1111/j.1528-1167.2009.02387.x
26. Whatley AD, Dilorio CK, Yeager K (2010) Examining the relationships of depressive symptoms, stigma, social support and regimen-specific support on quality of life in adult patients with epilepsy. Health Educ Res 25(4):575–584. https://doi.org/10.1093/her/cyq001

27. Gigli GL, Maschio M, Diomedi M, Placidi F, Silvestri G, Marciani MG (1996) Cognitive performances in newly referred patients with temporal lobe epilepsy: comparison with normal subjects in basal condition and after treatment with controlled-release carbamazepine. Int J Neurosci 88(1-2):97–107 https://doi.org/10.3109/00207459608999816
28. Wesnes KA, Edgar C, Dean AD, Wroe SJ (2009) The cognitive and psychomotor effects of remacemide and carbamazepine in newly diagnosed epilepsy. Epilepsy Behav 14(3):522–528. https://doi.org/10.1016/j.yebeh.2008.11.012
29. Sun W, Wang Y, Wang W, Wu X (2008) Attention changes in epilepsy patients following 3-month topiramate or valproate treatment revealed by event-related potential. Int J Psychophysiol 68(3):235–241. https://doi.org/10.1016/j.ijpsycho.2008.02.003
30. Duncan JS, Shorvon SD, Trimble MR (1990) Effects of removal of phenytoin, carbamazepine, and valproate on cognitive function. Epilepsia. 31(5):584–591. https://doi.org/10.1111/j.1528-1157.1990.tb06110.x
31. Pomara N, Lee SH, Bruno D, Silber T, Greenblatt DJ, Petkova E et al (2015) Adverse performance effects of acute lorazepam administration in elderly long-term users: pharmacokinetic and clinical predictors. Prog Neuro-Psychopharmacol Biol Psychiatry 56:129–135. https://doi.org/10.1016/j.pnpbp.2014.08.014
32. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R (2012) A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. Drugs Aging 29(8):639–658. https://doi.org/10.1007/BF03262280
33. Crowe SF, Barker MJ, Kalechstein A, Van Gorp W (2007) Benzodiazepines. In: Neuropsychology and substance use: state-of-the-art and future directions, pp 75–110
34. Chung JK, Nakajima S, Shinagawa S, Plitman E, Chakravarty MM, Iwata Y et al (2016) Benzodiazepine use attenuates cortical β-amyloid and is not associated with progressive cognitive decline in nondemented elderly adults: a pilot study using F(18)-florbetapir positron emission tomography. Am J Geriatr Psychiatry 24(11):1028–1039. https://doi.org/10.1016/j.jagp.2016.04.013
35. Lacey CJ, Salzberg MR, D'Souza WJ (2015) Risk factors for depression in community-treated epilepsy: systematic review. Epilepsy Behav 43:1–7. https://doi.org/10.1016/j.yebeh.2014.11.023
36. de Souza EA, Salgado PC (2006) A psychosocial view of anxiety and depression in epilepsy. Epilepsy Behav 8(1):232–238. https://doi.org/10.1016/j.yebeh.2005.10.011
37. Thapar A, Kerr M, Harold G (2009) Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures. Epilepsy Behav 14(1):134–140. https://doi.org/10.1016/j.yebeh.2008.09.004

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