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Antiepileptic drug effects on subjective and objective cognition

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Abstract

Rationale: Cognitive impairment is one of the most common complaints for persons with epilepsy (PWE). These impairments are not only associated with seizures, but are also regularly reported as adverse effects of antiepileptic drugs (AEDs). Previous studies have examined cognitive effects of both AED monotherapy and polytherapy, yet there is limited research on these differences with respect to both subjective and objective cognition. The current study uses data from previous research conducted by the Centers for Disease Control and Prevention (CDC)-sponsored Managing Epilepsy Well (MEW) Network collaborative. We used three distinct archival datasets from the following: (1) the HOBSCOTCH efficacy trial at Dartmouth-Hitchcock Medical Center (HOB-1), (2) the multisite replication trial (HOB-2), and (3) epilepsy self-management research conducted at the NYU School of Medicine.

Methods: This retrospective analysis combined baseline data from three datasets to determine how the number of AEDs and the type of AEDs were associated with subjective (patient-reported) and objective (examiner-assessed) cognition. Subjective cognition was captured using the

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Ethical standards

The Committee for the Protection of Human Subjects (CPHS) at Dartmouth College has approved this study (CPHS#: 31399). Approval by CPHS was based on the study's appropriate balance of risk and benefit to subjects and a study design in which risks to subjects are minimized. All human studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Specific national laws were also observed. Informed consent was obtained for all subjects prior to their inclusion in the study, and all details that might disclose the identity of the subjects under study were omitted.

Declaration of competing interest

On behalf of all the authors, the corresponding author states that there is no conflict of interest.

cognitive subscale of the Quality of Life in Epilepsy Inventory (QOLIE-31) in all three datasets (n = 224), while objective cognition was measured using the Repeated Battery for the Assessment of Neuropsychological Status (RBANS) in the HOB-1 dataset (n = 65) and the Brief Test of Adult Cognition by Telephone (BTACT) in the HOB-2 dataset (n = 91). Multivariable linear regression was utilized for our initial assessments, followed by propensity score matching to provide stronger control of covariates. Matching was based on significantly different covariates, such as education, depression, and history of prior epilepsy surgery. Nonparametric statistical tests were utilized to compare these matched subjects.

Results: Subjective cognitive impairment was significantly worse among individuals on polytherapy (2 + AEDs) compared with those on monotherapy (1 AED) (adjusted $p = 0.041$). These findings were consistent with our propensity score matched comparison of monotherapy and polytherapy, which indicated that polytherapy was associated with worse overall subjective cognition (adjusted $p = 0.01$), in addition to impairments on the RBANS (Total score $p = 0.05$) and specific subdomains of the BTACT (Episodic Verbal Memory $p < 0.01$, Working Memory $p < 0.01$, Processing Speed $p < 0.01$). Interestingly, older generation AEDs were associated with better language performance than newer generation and combined generation AED therapy (RBANS Language $p = 0.03$). These language-specific findings remained significant after controlling for the effects of topiramate and zonisamide ($p = 0.04$).

Conclusions: A greater number of AEDs is significantly and negatively associated with subjective and objective cognition in PWE, and is in line with previous research. Antiepileptic drug type did not, in itself, appear to be associated with subjective cognition. Our findings suggest that ineffective AEDs should be replaced, rather than introducing additional AEDs to a treatment regimen. Further, while subjective and objective cognition assessments were both sensitive at detecting differences based on AED status, the neuropsychological objective subdomains offer additional and specific insights into how cognition is impaired with AEDs.

Keywords

Antiepileptic drugs; Cognition; Epilepsy; Medication; Neuropsychology

1. Introduction

An estimated 20–50% of persons with epilepsy (PWE) experience cognitive problems [1]. These challenges are associated with many negative health outcomes, including low quality of life, high disability, and poor adherence to antiepileptic drugs (AEDs) prescribed to manage the control of seizures [2]. This is unsurprising considering the numerous factors that adversely impact cognition in PWE, such as seizure type and frequency, structural brain abnormalities, comorbid mood disorders, psychosocial factors, and adverse effects from AEDs that may exacerbate existing cognitive deficits [3]. Moreover, the side effects of AEDs may be more debilitating than the actual seizures, leading to a reduced quality of life [4].

Older generation AEDs, higher dosages of AEDs, and polytherapy are associated with worse overall side effects [5]. It has also been shown that each additional drug in a multidrug treatment regimen can lead to a reduction in objective cognitive performance [6,7]. These

findings are consistent with those of Feldman et al., which suggested that the number of AEDs is the second best predictor of subjective cognitive impairment, only after depressive symptom severity [8]. Of the cognitive domains impaired by AEDs, attention, vigilance, and psychomotor speed were most commonly reported to be influenced by AED therapy [1,9,10].

In the present study, we sought to provide a retrospective, comparative examination of the relationship between AED treatment regimens and their impact on cognitive functioning in PWE. Several past studies have documented the negative impact of AEDs on cognitive functioning, yet there are limited evaluations that have concurrently assessed the subjective and objective cognitive effects of AEDs [3,5,11–13]. This type of comprehensive evaluation is necessary because subjective and objective cognition were shown to be only weakly correlated in neurological disorders and may be measuring different domains entirely [14–18]. Further, these types of comparative AED studies are sparse, especially when focusing on the cognitive side effects of AEDs.

The main goal of this study was to identify specific subjective and objective cognitive domains that are most impacted by AED therapy. We hypothesized that a greater number of prescribed AEDs, and use of older generation AEDs, would be associated with worse subjective and objective cognitive functioning. We define older generation AEDs as medications that were approved for the treatment of epilepsy prior to 1993. We also expected to observe an interactive effect between the type (older generation versus newer drugs) and number of AEDs with respect to cognition, such that cumulative AED burden (older drug plus greater number of drugs) would be associated with worse cognitive functioning.

2. Methods

2.1. Participants

This cross-sectional study examined archival clinical trial data collected as part of self-management research conducted through the Managing Epilepsy Well (MEW) Network [19]. The MEW Network is a Centers for Disease Control and Prevention (CDC)-sponsored thematic research network that develops, tests, and disseminates self-management programs for PWE. Study data from sites within the Network have been collated into a repository known as the MEW Database (MEW DB) [20]. Our study leveraged three distinct, archival MEW DB datasets: 1) the HOBSCOTCH program efficacy trial conducted at Dart-mouth-Hitchcock Medical Center (HOB-1), 2) the multisite HOBSCOTCH replication trial conducted at four epilepsy centers in Northern New England (HOB-2), and 3) epilepsy self-management research conducted at the NYU School of Medicine (NYU). Data were obtained from baseline questionnaires that were administered prior to the introduction of any epilepsy self-management intervention, and pooled between the three datasets. Subjective cognition was captured using the cognitive functioning subscale of the Quality of Life in Epilepsy Inventory (QOLIE-31) short form in all three datasets (n = 235). All subjects on no AEDs were excluded, as they likely represented a different patient population. This resulted in a combined sample size of 224 PWE. Objective cognition was measured using the Repeated Battery for the Assessment of Neuropsychological Status (RBANS) in the HOB-1

dataset (n = 50) and the Brief Test of Adult Cognition by Telephone – modified (BTACT-m) in the HOB-2 dataset (n = 76). The HOB-2 dataset also contained scores from the Quality of Life in Neurological Disorders (NeuroQOL), another subjective cognitive assessment (n = 76). There was no objective cognitive assessment in the NYU dataset.

2.2. Measures

2.2.1. Subjective cognition scales

2.2.1.1. QOLIE-COG.: The Quality of Life in Epilepsy Inventory (QOLIE-31) was initially designed to assess the effect of treatment on epilepsy-associated issues and the patient's overall health-related quality of life (HRQOL) [21,22]. The measure contains 31 questions that examine the past four weeks of a patient's life. The questions are stratified into seven subscales, which include the following: seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning [23]. The cognitive functioning subscale (QOLIE-COG) scores are calculated based on the mean of items from the cognitive functioning subscale. The QOLIE-COG scores ranged from 0 to 100 with higher scores corresponding to better subjective cognitive functioning.

2.2.1.2. NeuroQOL-COG.: The Quality of Life in Neurological Disorders (NeuroQOL-COG Item Bank v2.0 Cognitive Function) is a brief validated tool developed by the National Institutes of Health (NIH) for assessing cognitive functioning in patients with neurological disease [24]. It consists of 28 5-point Likert scale questions. Total scores were calculated by dividing summed scores by the maximum score possible, then multiplying by 100. Higher scores corresponded to better subjective cognitive functioning.

2.2.2. Objective cognition scales

2.2.2.1. RBANS.: The RBANS was first developed by Randolph et al. in 1998 as an assessment tool for dementia [25]. The RBANS measures attention, language, visuospatial abilities, constructional abilities, immediate memory, and delayed memory. It consists of 12 subtests, which provide a total scaled score and five index scores. The mean subtest score is 100, with a standard deviation (SD) of 15. Higher subtest and overall scores correspond to better performance.

2.2.2.2. BTACT.: The BTACT was developed and validated as a neurocognitive assessment that is administered over the phone [26]. The following subtests were included in the present analyses as they assess the same domains as the RBANS: a single trial form, the Rey Auditory Verbal Learning Test (RAVLT), is administered to assess verbal episodic memory, which is followed after completion of other tests by a delayed recall trial. The RAVLT scores ranged from 0 to 15, with higher scores representing better performance. The 30 Seconds and Counting Task (30-SACT) assesses processing speed. Total 30-SACT scores were calculated with 100 − (number reached + number of errors), with higher total 30-SACT scores corresponding to better cognitive performance. The Category Fluency (CAT) subtest assesses executive function, semantic memory retrieval, verbal ability, and speed of processing. Higher CAT scores indicate better performance. The Number Series (NS) subtest examines inductive reasoning and fluid intelligence. The NS scores ranged from 0 to 5, and

the total NS score is averaged over trials, with higher averaged scores indicating better performance.

2.2.3. Other assessments

2.2.3.1. Patient Health Questionnaire-9 (PHQ-9).: The Patient Health Questionnaire-9 (PHQ-9) is based on the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV) criteria for major depressive disorder (MDD) [27]. Each of the nine items is rated on a 4-point scale from 0 to 3. The scale assesses depression two weeks prior to and including the day of survey completion [28]. The PHQ-9 is a well-validated scale for assessing depression in PWE, with scores ranging from 0 to 27. Higher scores correspond to greater depression severity [27,29].

2.3. Statistical analyses

Subjects were categorized into two groups based on AED number (1 AED, 2 + AEDs) for the univariate analysis. Subject characteristics were compared across these groups and across the three datasets (HOB-1, HOB-2, and NYU) using chi-square tests for categorical variables and Student's t-tests or analysis of variance (ANOVA) for continuous variables. A multivariable linear regression model (ANCOVA) was constructed with AED number as an associated factor of interest, subjective cognition scores (QOLIE-COG) as the outcome, and education, prior epilepsy surgery, seizure control, depression (PHQ-9 scores), and anxiety (anti-anxiety medication usage) as covariates. Our initial analysis was only performed for subjective cognition because this was the only measure that was consistent across all three datasets. In this study, seizure control referred to not having a seizure in the past 30 days.

In addition to ANCOVA, we utilized propensity score matching to optimize the statistical control of potential confounders and to enhance the interpretability of the observed results. This was crucial for our study, as it accounted for differences in the sample populations of the three datasets. We matched subjects on 1 AED to subjects on 2 + AEDs using the propensity to be on 1 AED to assess the comparative effect between monotherapy (1 AED) and polytherapy (2 + AEDs) for both the subjective and objective cognitive assessments. Propensity scores were calculated using logistic regression and matched using the nearest neighbors matching algorithm. propensity score matching (PSM) was based on education, depression (PHQ-9 score), anxiety (anti-anxiety medication use), seizure control, and history of prior epilepsy surgery. We then assessed these PSM groups with nonparametric tests, such as the two-sample Wilcoxon test. The PSM groups were also utilized to determine if AED generation was associated with differences in subjective and objective cognition. These PSM groups were evaluated using the nonparametric Kruskal–Wallis test. Bonferroni corrections were employed to account for multiple comparisons within each category (i.e., AED generation and cognition).

We performed a post hoc analysis to examine whether topiramate and zonisamide were driving the association observed between AED generation and language, as measured by the RBANS. We removed all PSM subjects containing either of these AEDs to determine if the effect would be mitigated and performed the nonparametric Kruskal-Wallis test. We also employed multivariable linear regression models to assess the five most commonly

prescribed AEDs (lamotrigine, levetiracetam, topiramate, carbamazepine, and lacosamide) with respect to the objective and subjective cognitive measurements that were significant in our previous AED number and AED generation analyses. These models were coded with a reference variable representing the median cognitive score for the corresponding measure and sought to assess any associations between specific AEDs and changes in cognition. Lastly, we developed multivariable linear regression models to assess potential interactions between AED number and AED generation. These models were well-powered with an average sample size of 126 and a range of 76 to 259. All models controlled for depression, anxiety, seizure control, education, and history of prior epilepsy surgery as potential confounders. The significance level was set at $p < 0.05$, and all statistical analyses were performed using R version 3.4.1.

3. Results

3.1. Demographic and univariate analyses

Demographic and clinical characteristics are reported in Table 1. Subjects had a mean age of 43.90 (range: 18–70, SD: 11.58), 60.71% were female, 37.95% were employed, and 37.10% were high school graduates. Within this sample, 20.51% had generalized idiopathic epilepsy as determined by a clinician, 61.80% had abnormal electroencephalographic findings, 35.76% had prior epilepsy surgery, and 45.74% had controlled epilepsy. Prior epilepsy surgery, seizure control, PHQ-9 score, anti-anxiety medication usage, and education were found to be significant confounders for the relationship between cognition and AED utilization. Table 2 lists the overall counts for each of the different AEDs in this study and is also stratified by monotherapy and polytherapy.

Our univariate analysis of AED number (1,2 + AEDs) and subjective cognition (QOLIE-COG) demonstrated that subjective cognition scores were significantly lower for subjects with 2 + AEDs than 1 AED ($p = 0.049$) (Fig. 1). This analysis was based on the total pooled sample of 234 PWE. These results were validated in our multivariable analysis, which accounted for the effects of potential confounders ($p = 0.041$).

3.2. PSM analyses of the number of AEDs

After PSM, there were 50 subjects from the HOB-1 dataset and 76 subjects from the HOB-2 dataset. The PSM analysis revealed that subjective cognition (QOLIE-COG) was significantly lower for polytherapy than monotherapy ($p = 0.01$) (Fig. 2). The NeuroQOL-COG, an additional measure of subjective cognition, also demonstrated a significant reduction in subjective cognition ($p < 0.01$). Table 3 depicts the PSM comparison of subjects from HOB-1 with the RBANS as the objective cognition outcome, in addition to the PSM comparison of subjects from HOB-2 with the BTACT as the objective cognitive outcome. There were no notable differences within the RBANS indices (immediate, visuospatial, language, attention, delayed), but polytherapy was associated with worse performance relative to monotherapy for the RBANS Total score ($p = 0.05$), as well as the CAT and NS subtests of the BTACT ($p < 0.01$).

3.3. PSM analysis of AED generation and assessment for interactions

Table 4 displays results from the PSM analysis of AED generation. There were no significant associations between AED generation and cognition for the HOB-2 PSM sample. There were, however, significant differences in the overall RBANS Total score ($p = 0.03$) and the RBANS language subtest ($p = 0.01$) in the HOB-1 PSM sample. The association between the generation of AED and the RBANS language subtest remained significant after removing all subjects on either topiramate or zonisamide ($p = 0.04$). In assessing the five most commonly prescribed AEDs, we failed to find any significant associations between a specific AED and cognition for both subjective and objective assessments ($p > 0.05$). Our other multiple linear regression model also demonstrated that there were no significant interactions between AED generation and AED number ($p > 0.05$).

4. Discussion

Cognitive dysfunction is one of the primary concerns for PWE, yet the best metric for assessing cognitive function in this population remains unclear. Our study assessed the relationship between AED number, AED type (newer generation versus older generation AEDs), and cognition utilizing previously validated measures of subjective and objective cognition. Our study demonstrated that AED number may have a greater negative impact on subjective and objective cognition than AED type. While this result is consistent with past literature, we provided novel insights into the specific cognitive domains that are most impacted by polytherapy during epilepsy treatment [30–33]. We also found that results from subjective and objective cognitive measures were concordant in their recommendations. This highlights the utility of both measures, despite reports that there is generally a limited relationship between the two ratings [8,13]. Our findings support Samarasekera et al.'s claim that both subjective and objective assessments of cognition contribute discretely to a comprehensive assessment of cognition [12].

The PSM method was employed to reduce the effects of confounding in the evaluation of cognitive assessments [34]. While the RBANS was only able to identify overall differences in objective cognition, the BTACT was able to detect differences in specific cognitive functions between those receiving monotherapy and polytherapy. In previous reports, attention, vigilance, and psychomotor speed were the major domains impacted by AED therapy [1,9,10]. Our subtest analysis of the BTACT augments these findings by illustrating a significant difference in Category Verbal Fluency and NS subtests associated with AED number. The BTACT Category Verbal Fluency subtest is thought to reflect executive function, semantic memory retrieval, verbal ability, and speed of processing, while the BTACT NS represents inductive reasoning and fluid intelligence [26,35–37]. These findings support the BTACT as a reliable measure for assessing cognition and highlight the cognitive domains most impacted by AED polytherapy. Thus, clinicians should strongly consider replacing an AED to maintain a monotherapy regimen, and consider concepts, such as "rational polytherapy", for managing complex epilepsy treatment regimens [38].

A particular question of interest was whether newer generation AED therapy was preferable to older generation AED therapy and combination therapy with respect to cognitive side effects. In assessing AED generation, the only notable differences were for the RBANS

Total score and the RBANS Language index score. Surprisingly, subjects on older generation AEDs performed better than subjects on both newer generation AEDs and combined AED treatment regimens. We validated these language-specific findings after removing subjects on either topiramate or zonisamide, as these AEDs were previously linked with diminished language performance [39]. Together, these findings suggest that older generation AEDs may have fewer language-related side effects than newer generation AEDs, and may be a potential option to consider, especially for AED monotherapy [40,41]. We would, however, like to consider the limited sample size after PSM, which may have limited our ability to detect other statistically significant trends between AED generation and cognition. We would also like to note that it is possible that PWE who have been successfully treated with and remain on first generation AEDs could represent a different population of PWE than those who may be prescribed newer agents. For example, some of the individuals on newer drugs might have failed previous trials of first- or second-generation AEDs. Thus, despite our cognitive findings, we do not discredit past reports that support newer generation AEDs, as they are associated with fewer pharmacokinetic drug–drug interactions and adverse effects [9,42,43].

We also evaluated if there were interactive effects between the number and generation of AEDs in a treatment regimen. Our regression analysis demonstrated that there were no significant interactions between AED number, AED generation, and cognition. These findings may be useful in clinical practice, as they indicate that AED number may be a stronger influencer of patient-reported and objective cognitive functioning than AED type. It may also emphasize the benefits of replacing an AED, rather than adding a new AED to the treatment regimen for PWE. From a clinical perspective, our results encourage providers to consider what patients deem to be the most concerning cognitive side effects, while deciding on whether to prioritize AED number or AED generation, to minimize the impact AEDs have on quality of life.

There are several limitations to this study. First, although our study pooled data from three datasets, the generalizability is limited to a Northeastern sample population, which had a relative underrepresentation of racial and ethnic minorities. There also could have been slight differences in the subject pools between studies, which may explain the discrepancy in the observed results between the HOB-1 and HOB-2 datasets. The dosage and blood levels of AEDs were also not accounted for in this study, as they were not available. The sample size of our PSM groups limited the power in our controlled assessment. Lastly, differences seen for the RBANS versus BTACT may be due to differences between the assessments, such as the mode of administration (face-to-face versus telephone) and the nature of the tests included in each battery of measures.

In summary, we observed that the number of AEDs in a treatment regimen was more strongly associated with changes in subjective and objective cognition than the generation of AEDs. Additionally, AED number was associated with worse performance on the measures of specific aspects of cognition, while older generation AEDs may be related to fewer language-related side effects than newer generation AEDs. From a clinical perspective, our results recommend switching AEDs, rather than adding an AED to the treatment regimen, to potentially limit the impact of such medications on cognitive functioning in PWE.

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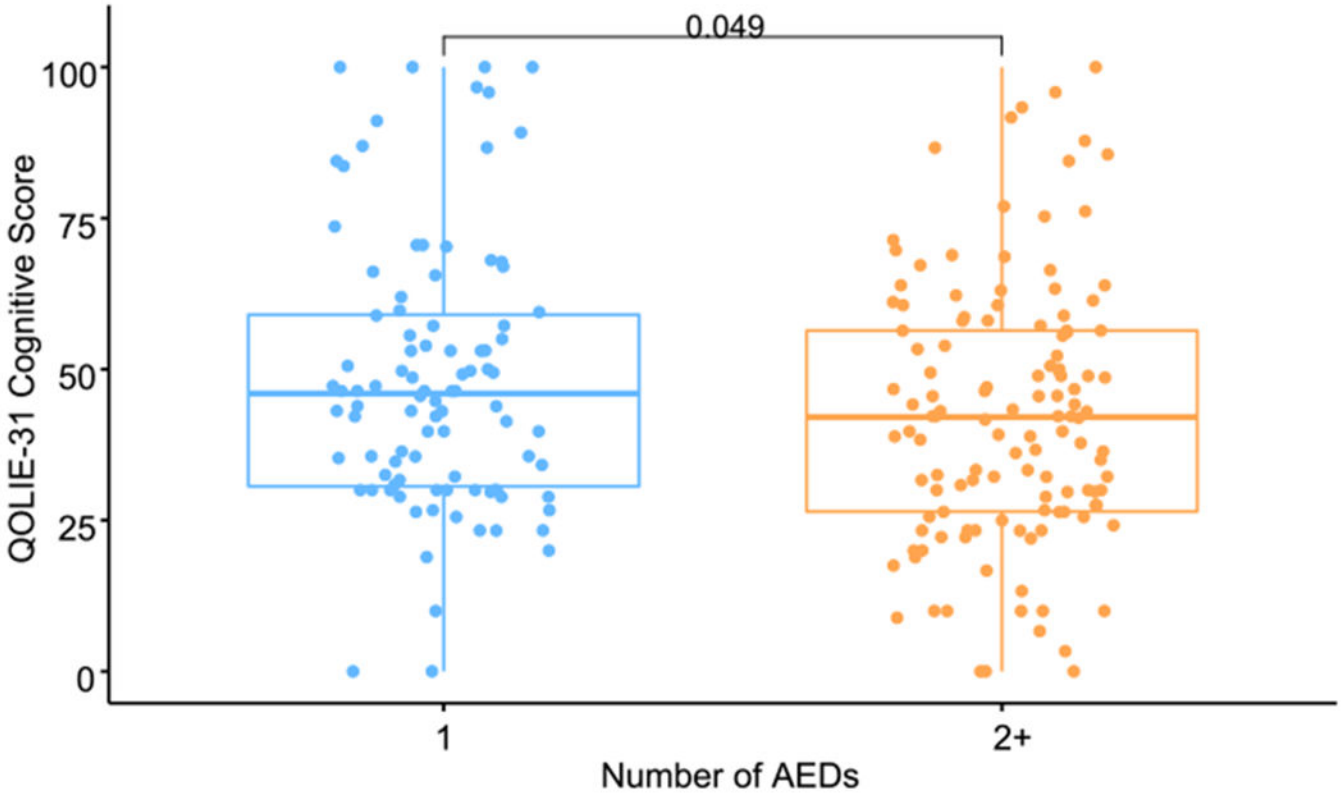

Fig. 1.

Influence of monotherapy and polytherapy on subjective cognition. Polytherapy was associated with lower QOLIE-31 subjective cognition scores ($p = 0.049$) even after adjusting for education, prior epilepsy surgery, seizure control, depression, and anxiety (adjusted $p = 0.041$).

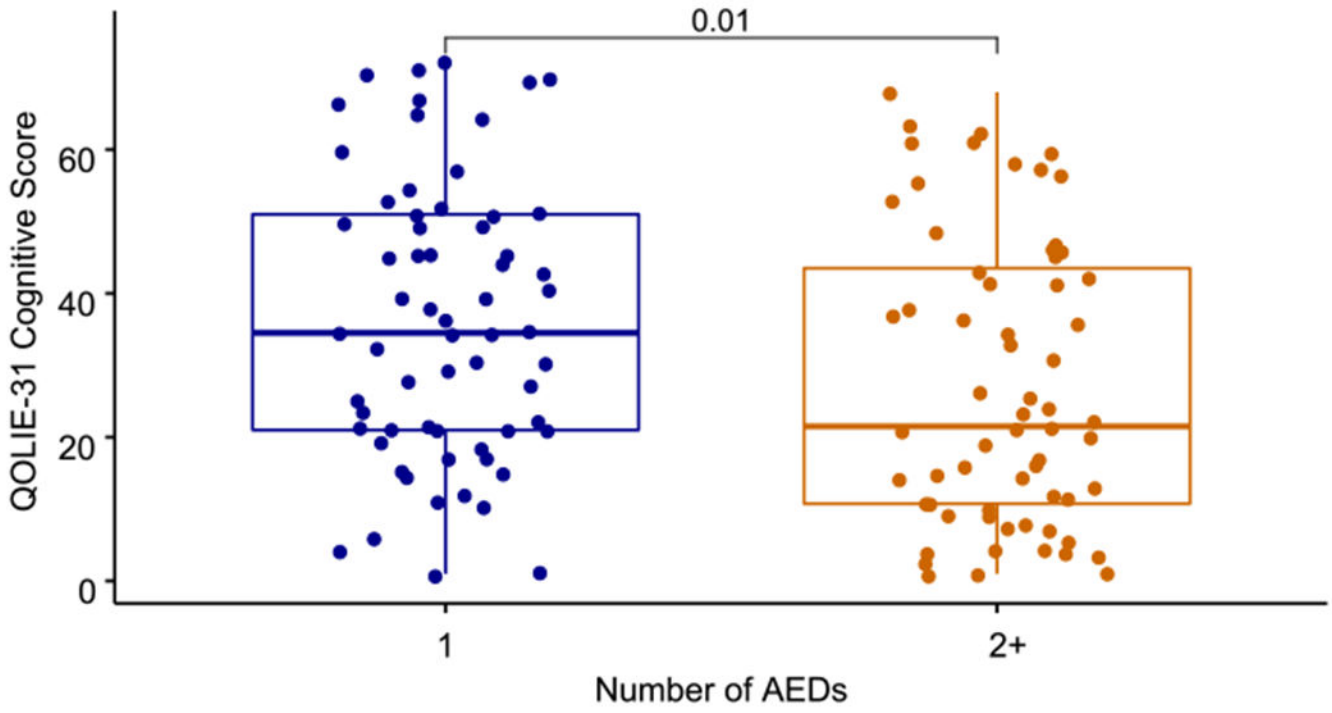

Fig. 2.

Propensity score matched comparison of monotherapy and polytherapy. Polytherapy was associated with a significant reduction in QOLIE-31 subjective cognition after propensity score matching ($p = 0.01$).

Table 1

Participant demographic and clinical characteristics.

	HOB-1 (n = 65)	HOB-2 (n = 91)	NYU (n = 68)	p-Value
Age (mean (SD))	45.58 (10.60)	46.92 (11.42)	38.16 (10.75)	<0.01
Gender (male %)	20 (30.8)	32 (35.2)	36 (52.9)	0.02
Uncontrolled seizures (%)[a]	25 (39.1)	30 (33.0)	66 (97.1)	<0.01
Education (%)				<0.01
High school graduate	32 (50.8)	18 (20.0)	32 (47.1)	
College graduate	31 (49.2)	69 (76.7)	20 (29.4)	
Other	0 (0.0)	3 (3.3)	16 (23.5)	
Unemployed (%)	41 (63.1)	52 (57.1)	46 (67.6)	0.394
Not able to drive (%)	33 (51.6)	33 (36.7)	NA	0.08
Idiopathic generalized epilepsy (%)	10 (15.4)	22 (24.2)	NA	0.24
No prior epilepsy surgery (%)	33 (54.1)	64(71.1)	NA	0.04
Abnormal EEG (%)[b]	20 (35.7)	69 (78.4)	NA	<0.01
Polytherapy (%)	36 (55.4)	53 (58.2)	38 (55.9)	0.927
Generation of AED				0.137
New	36 (56.2)	63 (70.0)	45 (68.2)	
Old	12 (18.8)	8 (8.9)	4 (6.1)	
Both	16 (25.0)	19 (21.1)	17 (25.8)	
No antidepressant medication (%)	38 (59.4)	53 (59.6)	NA	0.98
No anti-anxiety medication (%)	36 (55.4)	87 (95.6)	NA	<0.01
PHQ-9 score (mean (SD))[c]	9.60 (5.90)	9.27 (6.17)	NA	0.741

[a] Uncontrolled epilepsy refers to a patient that has had a seizure in the past 30 days.

[b] Electroencephalography revealed epileptiform or non-epileptiform abnormalities.

[c] Patient Health Questionnaire-9 total scores range from 0 to 27, with higher scores indicating an increased depression severity.

Table 2

Counts of antiepileptic drugs in the combined dataset (n = 224).

AED	Total n (%)	Monotherapy n (%)	Polytherapy n (%)
Lamotrigine	92 (23.53)	36 (37.50)	56 (18.98)
Levetiracetam	74 (18.92)	17 (17.71)	57 (19.32)
Carbamazepine[a]	37 (9.46)	13 (13.54)	24 (8.13)
Lacosamide	31 (7.93)	3 (3.12)	28 (9.49)
Topiramate	25 (6.39)	6 (6.25)	19 (6.44)
Zonisamide	24 (6.14)	7 (7.29)	17 (5.76)
Valproic acid[a]	23 (5.88)	4 (4.17)	19 (6.44)
Clonazepam	17 (4.35)	2 (2.08)	15 (5.08)
Oxcarbazepine	15 (3.84)	2 (2.08)	13 (4.41)
Phenytoin[a]	13 (3.32)	1 (1.04)	12 (4.41)
Gabapentin	12 (3.07)	2 (2.08)	10 (3.39)
Phenobarbital[a]	8 (2.05)	1 (1.04)	7 (2.37)
Felbatol	5 (1.28)	1 (1.04)	4 (1.35)
Clobazam	5 (1.28)	0 (0.00)	5 (1.70)
Primidone[a]	3 (0.77)	0 (0.00)	3 (1.02)
Perampanel	2 (0.51)	0 (0.00)	2 (0.68)
Brivaracetam	1 (0.26)	1 (1.04)	0 (0.00)
Vigabatrin	1 (0.26)	0 (0.00)	1 (0.34)
Felbamate	1 (0.26)	0 (0.00)	1 (0.34)
Pregabalin	1 (0.26)	0 (0.00)	1 (0.34)
Tiagabine	1 (0.26)	0 (0.00)	1 (0.34)
Total	391 (100)	96 (24.56)	295 (75.44)

[a]Denotes older generation antiepileptic drugs (AEDs).

Table 3

Propensity score matched comparison of the number of AEDs against cognition.

	1 AED	2+ AEDs	p-Value
HOB-1	n = 16	n = 34	
RBANS mean (SD)[a]			
Immediate	84.96 (15.95)	85.54(15.66)	0.97
Visuospatial	90.00 (14.10)	84.85 (17.87)	0.31
Language	91.08 (9.87)	84.11(14.86)	0.069
Attention	90.08 (22.67)	78.27(18.61)	0.096
Delayed	82.77 (18.81)	78.00 (19.47)	0.49
Total score	84.27 (14.44)	77.04 (13.62)	0.05*
QOLIE-COG mean (SD)[b]	37.20 (14.76)	41.12 (15.30)	0.63
HOB-2	n = 24	n = 52	
BTACT mean (SD)[c]			
30-SACT total score	38.37 (11.20)	35.44 (8.72)	0.13
CAT total score	20.74 (6.62)	16.26 (5.60)	<0.01*
RAVLT long recall	2.58 (2.10)	2.26 (1.70)	0.68
NS total	2.53 (1.27)	1.55 (1.18)	<0.01*
QOLIE-COG mean (SD)[b]	44.68 (18.10)	28.56 (16.56)	<0.01*
NeuroQOL mean (SD)[d]	63.16 (8.83)	53.66 (9.80)	<0.01*

[a]RBANS = Repeated Battery for the Assessment of Neuropsychological Status, with higher scores corresponding to better performance.

[b]QOLIE-COG = Quality of Life in Epilepsy – Cognition scores range from 0 to 100, with higher scores corresponding to better QOL.

[c]BTACT = Brief Test of Adult Cognition by Telephone, with higher scores indicating better performance for all subtests.

[d]NeuroQOL = Quality of Life in Neurological Disorders, with higher total scores corresponding to better cognitive functioning.

*Significant after Bonferroni correction.

Table 4

Propensity score matched comparison of AED generation against cognition.

	Generation			p-Value
	New	Old	Combined	
HOB-1	n = 27	n = 7	n = 16	
RBANS mean (SD)[a]				
Immediate	85.74 (14.81)	94.43 (17.62)	80.44 (16.01)	0.14
Visuospatial	83.07 (16.72)	96.14 (10.57)	85.75 (17.77)	0.16
Language	85.48 (11.94)	97.28 (10.95)	80.37 (14.56)	0.01*
Attention	78.37 (17.89)	99.57 (20.16)	81.62 (19.46)	0.07
Delayed	79.30 (18.00)	84.57 (24.70)	73.12 (21.18)	0.39
Total score	77.30 (13.32)	92.86 (15.88)	74.56 (13.37)	0.03*
QOLIE-COG mean(SD)[b]	38.70 (15.25)	34.84 (14.64)	41.83 (17.39)	0.66
HOB-2	n = 50	n = 7	n = 19	
BTACT mean (SD)[c]				
30-SACT total score	37.7 (9.75)	35.86 (11.94)	33.05 (7.76)	0.22
CAT total score	18.22 (6.49)	14.86 (6.12)	18.05 (6.43)	0.46
RAVLT long recall	2.64 (1.76)	1.57 (1.72)	1.95 (1.47)	0.13
NS total	2.18 (1.32)	1.71 (1.11)	1.79 (1.40)	0.35
QOLIE-COG mean(SD)[b]	36.82 (19.48)	41.63 (13.77)	31.98 (16.24)	0.44
NeuroQOL mean (SD)[d]	57.97 (10.75)	58.26 (7.95)	56.31 (8.55)	0.75

[a]RBANS = Repeated Battery for the Assessment of Neuropsychological Status, with higher scores corresponding to better performance.

[b]QOLIE-COG = Quality of Life in Epilepsy – Cognition scores range from 0 to 100, with higher scores corresponding to better QOL.

[c]BTACT = Brief Test of Adult Cognition by Telephone, with higher scores indicating better performance for all subtests.

[d]NeuroQOL = Quality of Life in Neurological Disorders, with higher total scores corresponding to better cognitive functioning.

*Significant after Bonferroni correction.