



Contents lists available at ScienceDirect

## Epilepsy &amp; Behavior

journal homepage: [www.elsevier.com/locate/yebeh](http://www.elsevier.com/locate/yebeh)

## The relationship between antiepileptic drug load and challenging behaviors in older adults with intellectual disability and epilepsy

Rosemary Monaghan<sup>a,b,\*</sup>, Máire O'Dwyer<sup>a</sup>, Retha Luus<sup>c</sup>, Niamh Mulryan<sup>c,d</sup>, Philip McCallion<sup>e</sup>, Mary McCarron<sup>c</sup>, Martin C. Henman<sup>a</sup>

<sup>a</sup> School of Pharmacy and Pharmaceutical Sciences, Trinity College, College Green, Dublin 2, Ireland

<sup>b</sup> The Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA), School of Nursing & Midwifery, Trinity College, College Green, Dublin 2, Ireland

<sup>c</sup> Trinity Centre for Ageing and Intellectual Disability, School of Nursing & Midwifery, Trinity College, College Green, Dublin 2, Ireland

<sup>d</sup> Daughters of Charity, Disability Support Services, St Vincent's Centre, Navan Rd, Dublin 7, Ireland

<sup>e</sup> School of Social Work, College of Public Health, Temple University, Philadelphia, PA, USA

### ARTICLE INFO

#### Article history:

Received 8 April 2021

Revised 16 June 2021

Accepted 24 June 2021

#### Keywords:

Epilepsy

Intellectual disability

Challenging behaviors

Antiepileptic drugs

AED load

### ABSTRACT

Antiepileptic drugs (AEDs) may affect mood and behavior in people with epilepsy and intellectual disability. A high AED load, derived from AED polytherapy and/or high doses of AEDs, has been suggested to be a risk factor for behavioral side effects. Data were drawn from Wave 3 of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). The Behavior Problems Inventory Short Form (BPI-S) was used to assess challenging behaviors. AED load was calculated and median AED loads obtained. Non-parametric tests and binary logistic regression were performed to determine the relationship between AED load and challenging behaviors. Of participants with a reported diagnosis of epilepsy who were taking a regular AED and had completed BPI-S ( $n = 142$ ), 62.7% ( $n = 89$ ) exhibited challenging behaviors. Challenging behavior was found to be more prevalent in those with more severe levels of intellectual disability ( $p < 0.001$ ). Aggressive/destructive behavior and stereotyped behavior were significantly more likely in participants living in residential/campus settings. For participants with a severe/profound intellectual disability, a significantly higher median AED load was found for participants exhibiting aggressive/destructive behavior and self-injurious behavior (SIB) compared to participants not exhibiting these behaviors, indicating a high AED load may contribute to some behavioral problems in this population group. However, many factors can influence behavioral outcomes, creating difficulties in determining those that are associated and the nature of the association. Careful monitoring of AED load, together with increased vigilance for breakthrough behavioral issues is essential for dealing with these complex cases. Larger studies are needed to account for the potential confounding factors.

© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

### 1. Introduction

The burden of epilepsy is associated with psychiatric, cognitive, and behavioral comorbidity [1,2], factors more prevalent in people with intellectual disability [2]. Challenging behaviors occur in over 50% of people with intellectual disability, and are severe in 10% [3,4]. Self-injurious behavior (SIB), aggression, destruction, disruptive, and stereotyped behavior are frequently observed, resulting sometimes with the person being excluded from services or activities, or subjected to restrictive practices [5–7]. The etiology of challenging behavior is multifactorial, including physical symp-

toms, for example, constipation, pain; behavioral phenotypes; psychiatric disorders; psychological or social factors; and attention seeking, and avoidance behaviors [6]. A meta-analytic study examining risk factors for challenging behavior in people with intellectual disability found people with severe/profound intellectual disability were more likely to exhibit challenging behaviors (self-injury and stereotypy) compared to those with a mild/moderate level of intellectual disability [8].

Systematic reviews examining epilepsy as a possible marker [5] for challenging behaviors in people with intellectual disability have yielded inconclusive results [2,5,9,10], with some studies showing an increased prevalence in people with epilepsy and additional factors such as seizures of greater frequency and/or severity, medication side effects, and generalized EEG activity [10]. A meta-analysis of studies of adults with intellectual disability showed a

\* Corresponding author at: School of Pharmacy and Pharmaceutical Sciences, Trinity College, College Green, Dublin 2, Ireland.

E-mail address: [monaghar@tcd.ie](mailto:monaghar@tcd.ie) (R. Monaghan).

significantly higher rate of challenging behaviors in the epilepsy group compared with the non-epilepsy group, and a significantly higher rate of aggression and SIB in the epilepsy group [9]. However, the authors suggested that the effects may not be clinically significant because of small effect sizes [9].

Antiepileptic drugs (AEDs) may also affect mood and behavior in people with epilepsy [11] and intellectual disability [12]. The psychotropic effects of AEDs arise from the AEDs' mechanism of action (GABA or glutamate), underlying neurological condition and familial or personal history of psychiatric disorders [13,14]. Antiepileptic drugs with mood stabilizing properties (valproic acid, carbamazepine, lamotrigine) [15] are known to have positive effects on mental health and are used in the treatment of bipolar disorder [16]. However, lamotrigine has been reported to cause aggression in people with intellectual disability [17]. Other AEDs associated with a higher risk of precipitating challenging behaviors in people with intellectual disability include clobazam, clonazepam, levetiracetam, phenobarbital, perampanel, topiramate, tiagabine, vigabatrin, and zonisamide [9].

It is also suggested that people with epilepsy have a greater susceptibility to adverse behavioral effects of AEDs [16]. Levetiracetam has been known to incite aggressive behavior and irritability [11]. A systematic review examining the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials found adverse behavioral effects occurred significantly more frequently among patients with epilepsy compared to patients with cognition or anxiety difficulties being treated with levetiracetam [18].

Negative behavioral effects of AEDs may be associated with a higher AED load [12]. Total drug load has been defined as "the amount of drug exposure for a certain indication" [19]. Total AED load can be quantified as the sum of the prescribed daily dose (PDD) divided by the defined daily dose (DDD) (average maintenance dose) ratios (PDD/DDD) for each AED prescribed [20]. Use of AED polytherapy and high doses with rapid titration is associated with greater adverse cognitive and behavioral effects [21,22]. Indeed, consensus guidelines rank the impact of AEDs on behavior and cognition as second out of 11 priority areas [23].

The aim of this study was to examine the prevalence of challenging behaviors and its relationship with AEDs and AED load, in older adults with intellectual disability who report a diagnosis of epilepsy.

The objectives of this study were:

- (a) To describe the demographic characteristics of older adults with intellectual disability reporting a diagnosis of epilepsy and exhibiting challenging behaviors.
- (b) To examine the clinical characteristics of participants in this epilepsy cohort, exhibiting SIB, aggressive/destructive and/or stereotyped behavior, and the patterns of AED use, type of AED therapy, AED load, and co-prescribed psychotropic drugs.
- (c) To examine the relationship between AED load and demographic and clinical characteristics and investigate its association with exhibiting SIB, aggressive/destructive, and stereotyped behavior.

## 2. Methods

### 2.1. Study design

The data for this study were drawn from Wave 3 (2016/2017) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). IDS-TILDA is a nationally representative, longitudinal study of older adults with intellectual disability in Ireland aimed at investigating the aging profile, physical and

behavioral health, medication use, health service needs, social networks, living situations, community participation, and employment [24]. The original sample (Wave 1) was randomly selected using the National Intellectual Disability Database (NIDD) of Ireland, a database that gathers information on people with intellectual disability that use or are entitled to avail of services. Inclusion criteria consisted of age  $\geq 40$  years with intellectual disability (to reflect the lower longevity of people with intellectual disability), to be registered with the NIDD and to provide written consent to participate and/or family/guardian written agreement if required.

### 2.2. Participants

A total of 753 people aged between 41 and 90 years with intellectual disability were recruited in Wave 1 (2009/2010) following consent and protocol completion, representing 8.9% of people aged 40 years and over who were registered on the 2008 NIDD database [24]. If an individual could not provide consent themselves, a family member or guardian could sign a letter of agreement for their relative to participate. McCarron et al. undertook a comparison of demographics, showing the IDS-TILDA sample to be representative of this population group [25]. Level of intellectual disability is associated with intelligence quotient scores [26] – mild (50–69), moderate (35–49), severe (20–34) and profound (<20). Case notes for each participant where possible, confirmed the correct classification. For this study, the number of people taking part in Wave 3 was 609 with 44.2% male and 55.8% female [27]. The age range for Wave 3 was 48–95 years with a mean of 59.1 years (SD: 8.81) [27]. Overall in Wave 3, 24.8% had a mild intellectual disability, 46.2% a moderate intellectual disability, and 29.1% a severe/profound intellectual disability [27]. Participants live independently/with family, in community group homes, or in residential/campus settings. The response rate for Wave 2 (2013/2014) respondents who were alive at Wave 3 was 95.5% [27].

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standardized reporting guidelines for cross-sectional studies [28]. The IDS-TILDA study received ethics approval from the Faculty of Health Sciences, Ethics Committee at Trinity College Dublin and 138 intellectual disability service providers. To comply with the General Data Protection Regulation (GDPR) and the Irish Health Research Regulations (2018), a consent declaration waiver was obtained for the study from the Irish Health Research Consent Declaration Committee (HRCDC), for any data supplied in the past or future by people unable to consent themselves.

### 2.3. Measures

A pre-interview questionnaire (PIQ) was sent to each participant one week prior to the interview. This gave participants time to prepare and locate any information that may be needed (e.g., medication data), enhancing the reliability of the data. CAPI (Computer Assisted Personal Interviewing) interviews were completed by trained field workers, experienced in working with people with intellectual disability, utilizing laptops to answer the study questions. Advantages included the automatic rerouting of questions and detection of inadmissible replies. Different interviewing styles were undertaken by participants depending on their level of intellectual disability and capacity to communicate. There were three styles of interviewing; self-report, proxy assisted (where the person with intellectual disability answered some but not all questions), and proxy only, where the carer/support person answered the questions on the persons' behalf. To act as a proxy, the individual was required to know the person with intellectual disability for a minimum of six months. In terms of questions relating to epilepsy and the focus of this study, 20.8% of interviews were self-

report only, 48.5% used a proxy interview style, and 30.7% used a combination of self-report and proxy style [29].

#### 2.4. Report of a diagnosis of epilepsy

During Wave 1 data collection, each participant/proxy was asked in the PIQ if the individual with intellectual disability was ever diagnosed by a doctor/relevant health professional with epilepsy. In the face-to-face interview, confirmation of a report of a diagnosis of epilepsy and medications in the PIQ were made. In successive Waves (2 and 3) of the study, each participant/proxy was asked 'since your last interview, has a doctor ever told you that you have epilepsy?'. Consequently, a variable for prevalence was created [29]. Following reported epilepsy diagnosis confirmation, subsequent questions were asked regarding the reported diagnosis e.g., 'When were you first told by a Doctor that you had epilepsy?'. Additional free text detailed and confirmed any additional information. Reported epilepsy diagnosis data were not available for one (0.2%) participant with medication data (Fig. 1) [29].

#### 2.5. Medication exposure

Participants were asked which medications they take on a regular basis including prescribed, over-the-counter, and herbal medicines [30]. Medicines were recorded on the PIQ as either brand or generic name/International non-proprietary name, dose, frequency, route of administration, and date when medication was commenced. At the time of interview, trained interviewers checked all medication data for accuracy. Medications were coded using the World Health Organization Anatomical Therapeutic Chemical Classification (ATC) System by two pharmacists JOC and HA [29]. For Wave 3, medication data were available for 549 (90.1%) participants (Fig. 1). Of the 60 participants missing medication data, 4 (6.7%) participants refused to provide these data. Fifteen (25%) participants and/or proxies did not return the PIQ which contained the medication record detailing the participants' medication usage. Medication data were not available for the remaining 41 (68.3%) participants [29]. The author (RM) reviewed and confirmed all medication entries in this study.

#### 2.6. Drug class categorization

Antiepileptic drugs were defined as those with the ATC code N03A. All AEDs were split into those taken by a participant with a reported diagnosis of epilepsy and those without a reported diagnosis [29]. Clobazam was included in the AED category as it is primarily used for epilepsy. Midazolam was excluded from the N05C class as it is used for acute seizure control only [31]. Regular AEDs were then categorized into number of AEDs prescribed and subsequently into 'monotherapy' and 'polytherapy' [29]. Antiepileptic polytherapy was defined as concurrent treatment with two or more regular AEDs. Drugs indicated for the emergency treatment of acute seizures were recorded separately from the other AEDs and included midazolam.

Psychotropic co-medication examined were antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics & sedatives (N05C), drugs for dementia (N06D), and anticholinergic drugs (N04A). Lithium was classified as a mood stabilizer and prochlorperazine was not included in the antipsychotic category as all the doses reported in this study fell within the recommended range used for the treatment of Meniere's syndrome, labyrinthitis, and nausea and vomiting (10–40 mg daily).

#### 2.7. AED load

The AED PDD/DDD ratio [19,32] was calculated for all participants with medication data taking a regular AED. Due to incomplete dosage data for six participants (excluded from analysis), this ratio was calculated for 96.6% (168/174) of those with a reported diagnosis of epilepsy and taking a regular AED in this study. The PDD/DDD ratio is the ratio of prescribed daily dose (PDD) to defined daily dose (DDD) [15]. The DDD is the assumed average maintenance daily dose, for a drug taken for its main indication in adults [15] (Supplementary Table 9). The PDD is the actual prescribed daily dose. A PDD/DDD ratio can be used as a measure of drug load [15]. This analysis was completed using Microsoft Excel and a cumulative ratio of all AEDs being taken, calculated.

$$\text{total drug load} = \sum_i \frac{PDD_i}{DDD_i}$$

Numerical descriptive measures, namely median and interquartile range (IQR), of the total AED load variable were obtained and analyzed.

#### 2.8. Challenging behaviors

The Behavior Problems Inventory-Short Form (BPI-S), an informant-based questionnaire, was used to assess challenging behaviors [33]. The instrument examines three subtypes of challenging behaviors; self-injurious behavior (SIB) (8 items), aggressive/destructive behavior (10 items), and stereotyped behavior (12 items) [34] (Supplementary Table 2). A study investigating reliability and factorial validity of the BPI-S found acceptable reliability regarding internal consistency, inter-rater agreement, and test-retest reliability [34]. This section was completed by the carer/key worker/support person who knew the person with intellectual disability very well (minimum of 6 months). These data were collected via the PIQ, giving the informant time to fill out the information required prior to the CAPI interview. Broad definitions of each type of behavior were given in the PIQ (Supplementary Table 10).

Individuals providing these data were instructed to describe behaviors in the person with intellectual disability during the previous two months:

1. How often a described behavior typically occurs.
2. How serious a problem the behavior is.

If the behavior did not occur during the previous two months and therefore, posed no problem, they were instructed to check "never/no problem". If the behavior had occurred, they were asked to rate the approximate frequency of its occurrence and its severity. Each level of severity (mild/moderate/severe) was clearly defined. They were not required to provide a severity level for stereotyped behavior and no scale/severity definition was provided. For the purpose of this study, a positive response to frequency indicated the presence of challenging behaviors. This allowed for the creation of a variable (YES/NO) for individual types of behaviors which were grouped into SIB, aggressive/destructive, and stereotyped behavior per the BPI-S scale [33] and then grouped into overall presence of challenging behaviors.

#### 2.9. Covariates

Covariates investigated were gender (male/female), age (<50/50–64/65+ years), level of intellectual disability (mild/moderate/severe/profound/unverified), place of residence (independent/family/community group home/residential/campus), cause of

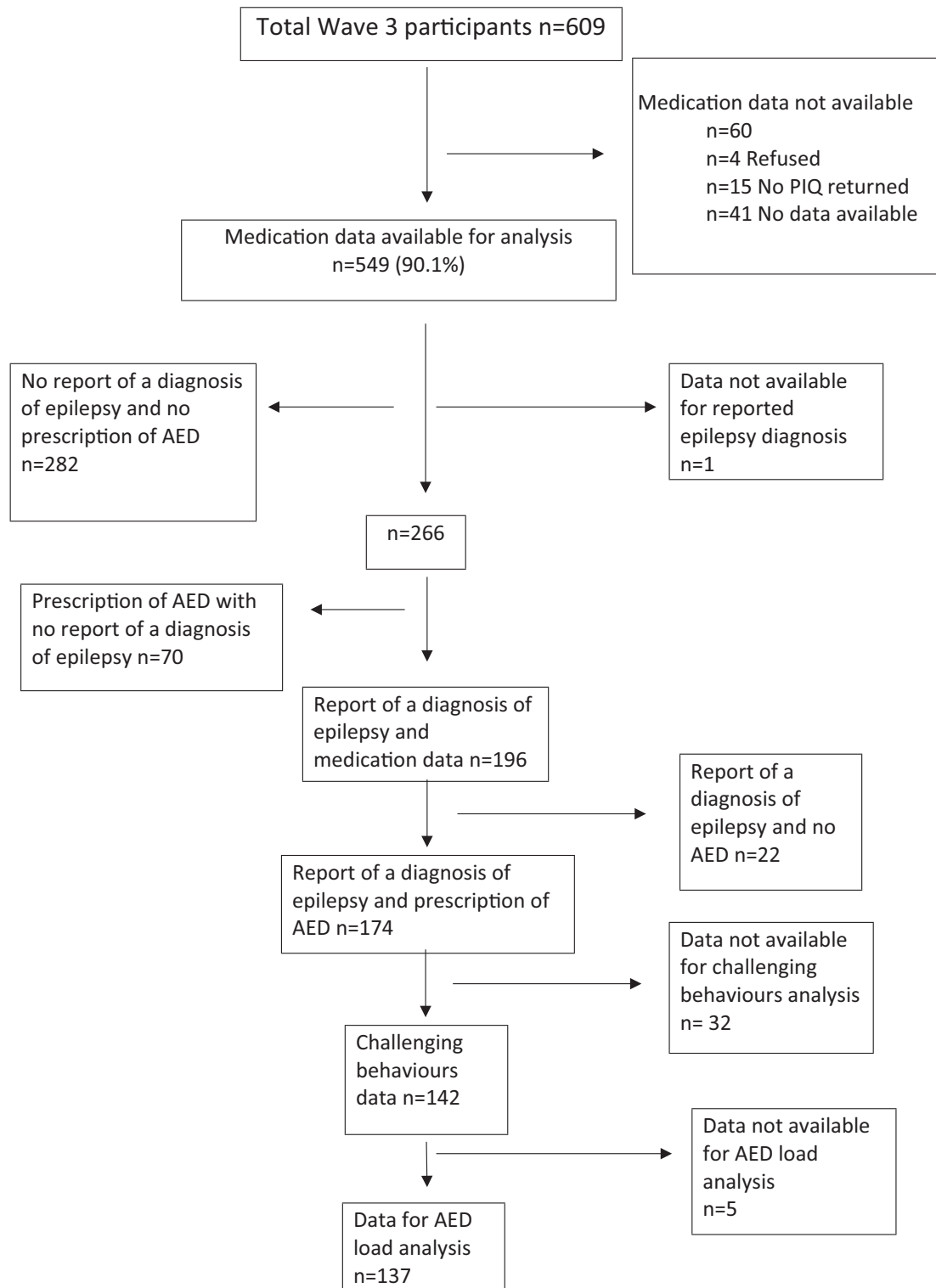


Fig. 1. Flow chart of epilepsy diagnosis, challenging behavior and AED use.

intellectual disability (Down Syndrome/other etiology/unknown cause), psychotropic medications (antipsychotics/antidepressants/lithium/anxiolytics/hypnotics and sedatives/drugs for dementia/anti-cholinergic), comorbid mental health conditions, any challenging behaviors, categorized challenging behaviors (SIB/aggressive/destructive/stereotyped behavior), type of seizures (generalized/other), seizure frequency (none in the last year/at least one in the last year), and AEDs. Psychotic disorder includes

reported doctor's diagnosis of hallucinations, schizophrenia, and psychosis. Mood disorder includes reported doctor's diagnosis of depression, manic depression, mood swings, and emotional problems and anxiety disorder includes reported doctor's diagnosis of anxiety and Post-Traumatic Stress Disorder (PTSD), although there were no reports of PTSD in this study [29].

Mood stabilizing AEDs include valproic acid, carbamazepine, and lamotrigine. The categorized seizure type was based on the

2017 International League Against Epilepsy (ILAE) classification of seizures [35]. Generalized seizures include tonic-clonic, tonic, clonic, atonic, myoclonic, and absence. Focal seizures include simple partial seizures and complex partial seizures. 'Other' seizure category includes both focal and unknown seizures due to low numbers of reported focal seizures ( $n = 3$ ).

Residential/campus settings were defined as living arrangements where 10 or more people share a single living unit or where the living arrangements are campus based. Community group homes are in a community setting with staff support for small groups of people with intellectual disabilities.

## 2.10. Statistical analyses

Descriptive statistics described the characteristics of the population being studied. The Chi Squared ( $\chi^2$ ) test for independence was used to test for significant association between categorical variables at bivariate level. Fisher's Exact test was used to test for significant association between categorical variables where the sample size in subgroups was small ( $n < 5$ ). To control for problems associated with multiple comparisons, thereby increasing the likelihood of Type 1 error (rejecting the null hypothesis when it is true and the false discovery rate), a Bonferroni correction was applied to all bivariate Chi Squared/Fisher's Exact tests [36]. Variables that had small numbers in their subgroups were collapsed. This included type of residence, where participants who lived independently or with family were collapsed with participants living in community group homes. Participants with severe intellectual disability and profound intellectual disability were collapsed into a single group of severe/profound intellectual disability. The Kolmogorov–Smirnov test and Shapiro–Wilk test were used to assess if the numerical variable for AED load (PDD/DDD) was normally distributed. As the AED load data significantly deviated from a normal distribution, the non-parametric test, Mann–Whitney  $U$ , was used to analyze the numerical data for AED load. Descriptive statistics, including medians (with 95% CI) and interquartile range (IQR) were used to describe the groups. Levene's test for homogeneity of variance was used to assess this assumption for non-parametric tests.

Three binary logistic regressions were performed to identify factors associated with exhibiting (a) SIB, (b) aggressive/destructive behavior, and (c) stereotyped behavior. In the three models, the possible outcomes for the dichotomous dependent variable were exhibiting (a) SIB yes/no, (b) aggressive/destructive behavior yes/no, or (c) stereotyped behavior yes/no. All the variables were entered into each regression model simultaneously. Demographic variables included in each of the models were age, level of intellectual disability, and place of residence. Antiepileptic drug load was included in the models as this was of interest in the study and following positive associations found in non-parametric tests undertaken. Small case numbers prohibited other demographic (for example, gender) and clinical variables (for example, type of seizures) from being included. The variance inflation factor (VIF) was utilized to test for multicollinearity between independent variables. All variables were found to have a VIF below the designated threshold of  $>2$  indicating no multicollinearity. The logistic regression results are presented as odds ratios with corresponding 95% confidence intervals.

The sample size for the logistic regression was determined using the guidelines of Peduzzi et al. namely that  $n = 10 k/p$  where  $k$  is the number of covariates (independent variables),  $p$  is the smallest of the proportions of negative or positive cases in the population, and  $k/p$  is the number of events per variable [37]. Four covariates ( $k$ ) were included in the three models and  $p$  was (a) SIB (exhibit)–  $52/141 = 0.369$ , (b) aggressive/destructive behavior (exhibit)–  $54/137 = 0.394$ , and (c) stereotyped behavior (do not

exhibit)–  $70/141 = 0.496$ . Therefore, the minimum numbers of cases needed ranged from  $n = 81$ – $108$ . The samples used here for each logistic regression ( $n = 125$ – $129$ ) exceeded these minimum requirements.

All statistical analyses were carried out using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at  $<0.05$ .

## 3. Results

### 3.1. Demographic & clinical characteristics of participants

Of participants with a reported diagnosis of epilepsy, taking at least one regular AED and having completed BPI-S ( $n = 142$ ), challenging behaviors were found to be exhibited by 62.7% ( $n = 89$ ) (Table 1). The level of intellectual disability was found to be significantly associated with exhibiting challenging behaviors ( $p < 0.001$ ) with a higher prevalence of challenging behaviors associated with greater severity of intellectual disability. Most participants (70.8%, 63 of 89) exhibiting challenging behaviors lived in a residential/campus setting. Of those exhibiting challenging behaviors, 52.8% reported taking AED polytherapy. The median AED load for participants exhibiting challenging behaviors was 1.26 (95%CI 0.93–1.66) compared with 1.30 (95%CI 0.80–1.76) for participants not exhibiting challenging behaviors. Of those exhibiting challenging behaviors, 39.3% ( $n = 35$ ) reported suffering from a mood disorder and 7.9% ( $n = 7$ ) a psychotic disorder. Reporting an anxiety disorder was found to be significantly associated with exhibiting challenging behaviors (41.6%,  $n = 37$ ,  $p = 0.022$ ). Half of the participants (49.4%;  $n = 44$ ) exhibiting challenging behaviors reported prescription of antipsychotics compared to a quarter (24.5%;  $n = 13$ ) of participants not exhibiting challenging behaviors ( $p = 0.003$ ).

### 3.2. Demographic & clinical characteristics of participants with categorized challenging behaviors

Participants exhibiting SIB (61.5%;  $n = 32$ ;  $p = 0.001$ ) or stereotyped behavior (59.7%;  $n = 40$ ;  $p < 0.001$ ) were more likely to have a severe/profound level of intellectual disability. Over 70% of participants exhibiting each behavior type lived in residential/campus settings. The highest median AED load was found in participants exhibiting aggressive/destructive behavior (1.47, 95%CI 1.00–2.13) with the lowest median AED load found in participants exhibiting stereotyped behavior (1.09, 95%CI 0.70–1.57). Antipsychotics were reported for over half of participants exhibiting categorized challenging behaviors with 55.8% ( $n = 29$ ) of those exhibiting SIB ( $P = 0.005$ ), 57.4% ( $n = 31$ ) exhibiting aggressive/destructive behavior ( $p = 0.001$ ), and 53.5% ( $n = 38$ ) exhibiting stereotyped behavior ( $p = 0.001$ ) reporting prescription of antipsychotics (Table 2).

### 3.3. Relationship between AED load, demographic and clinical characteristics with regard to exhibiting SIB, aggressive/destructive, and stereotyped behavior

A significantly higher median AED load was found for participants with a severe/profound intellectual disability exhibiting aggressive/destructive behavior ( $p = 0.001$ ) (1.55, 95%CI 1.33–3.34) (Supplementary Table 7) and SIB ( $p = 0.048$ ) (1.42, 95%CI 1.00–1.67) (Supplementary Table 6), compared to not exhibiting aggressive/destructive behavior (0.64, 95%CI 0.53–1.30) and SIB (0.71, 95%CI 0.53–1.47). A significantly higher median AED load ( $p = 0.007$ ) was also found for participants taking AED monother-

**Table 1**  
Bivariate analysis of exhibiting challenging behaviors among those with a reported epilepsy diagnosis, taking a regular AED & completed BPI-S (n = 142).

Characteristic	Total n = 142	Exhibit challenging behaviors n = 89	Does not exhibit challenging behaviors n = 53	P value
<b>Gender</b>				0.043
Male	61 (43.0)	44 (49.4)	17 (32.1)	
Female	81 (57.0)	45 (50.6)	36 (67.9)	
<b>Age</b>				0.203
<50 years	16 (11.3)	13 (14.6)	3 (5.7)	
50–64 years	95 (66.9)	59 (66.3)	36 (67.9)	
65+ years	31 (21.8)	17 (19.1)	14 (26.4)	
<b>Level of intellectual disability</b>	n = 134	n = 85	n = 49	<b>&lt;0.001*</b>
Mild	21 (15.7)	6 (7.1)	15 (30.6)	
Moderate	53 (39.6)	31 (36.5)	22 (44.9)	
Severe/Profound	60 (44.8)	48 (56.5)	12 (24.5)	
<b>Place of residence</b>				0.003
Independent/Family/Community group home	55 (38.7)	26 (29.2)	29 (54.7)	
Residential/Campus	87 (61.3)	63 (70.8)	24 (45.3)	
<b>Cause of intellectual disability</b>	n = 140	n = 87	n = 53	0.397
Down Syndrome	19 (13.6)	14 (16.1)	5 (9.4)	
Other etiology	38 (27.1)	21 (24.1)	17 (32.1)	
Unknown etiology	83 (59.3)	52 (59.8)	31 (58.5)	
<b>Type of seizures</b>				0.935
Generalized	81 (57.0)	51 (57.3)	30 (56.6)	
Other	61 (43.0)	38 (42.7)	23 (43.4)	
<b>Seizure frequency</b>	n = 139	n = 87	n = 52	0.208
None in last year	79 (56.8)	53 (60.9)	26 (50.0)	
At least one in last year	60 (43.2)	34 (39.1)	26 (50.0)	
<b>Type of therapy</b>				0.380
Monotherapy	63 (44.4)	42 (47.2)	21 (39.6)	
Polytherapy (Median = 2, Max = 5)	79 (55.6)	47 (52.8)	32 (60.4)	
<b>Median AED load (PDD/DDD) (95% CI) (n = 137)</b>	1.30 (1.00–1.53)	1.26 (0.93–1.66)	1.30 (0.80–1.76)	0.984 <sup>b</sup>
<b>Mood stabilizing AED</b>				1.000 <sup>a</sup>
Yes	129 (90.8)	81 (91.0)	48 (90.6)	
No	13 (9.2)	8 (9.0)	5 (9.4)	
<b>Comorbid mental health disorder</b>				
Psychotic disorder	11 (7.7)	7 (7.9)	4 (7.5)	1.000 <sup>a</sup>
Mood disorder	48 (33.8)	35 (39.3)	13 (24.5)	0.071
Anxiety disorder	49 (34.5)	37 (41.6)	12 (22.6)	<b>0.022*</b>
<b>Co-prescribed psychotropic drugs</b>				
Antipsychotics	57 (40.1)	44 (49.4)	13 (24.5)	0.003
Antidepressants	45 (31.7)	28 (31.5)	17 (32.1)	0.939
Anxiolytics	25 (17.6)	20 (22.5)	5 (9.4)	0.048
Hypnotics & sedatives	19 (13.4)	13 (14.6)	6 (11.3)	0.578
Lithium	4 (2.8)	4 (4.5)	0 (0)	0.297 <sup>a</sup>
Drugs for dementia	4 (2.8)	3 (3.4)	1 (1.9)	1.000 <sup>a</sup>
Anti-cholinergic (N04A)	16 (11.3)	11 (12.4)	5 (9.4)	0.594

P value: Chi Square, <sup>a</sup> Fisher Exact Test (2 sided), <sup>b</sup> Mann Whitney U mean rank- exhibit challenging behavior = 68.95 (n = 86), do not exhibit challenging behavior = 69.00 (n = 51). P value: for Chi-Square Test after applying Bonferroni correction  $\alpha = 0.05/20 = 0.0025$  thus  $p < 0.0025$  for significance. Statistically significant results (after applying Bonferroni correction) marked in bold and with an asterisk \*.

apy and exhibiting SIB (0.67, 95%CI 0.60–0.93) compared to not exhibiting SIB (0.57, 95%CI 0.40–0.67).

In addition, a significantly higher median AED load ( $p = 0.006$ ) was found for participants reporting at least one seizure in the last year and exhibiting aggressive/destructive behavior (3.62, 95%CI 2.67–5.07), compared to not exhibiting aggressive/destructive behavior (1.75, 95%CI 1.17–2.73). Participants not reporting antipsychotics and antidepressants and exhibiting aggressive/destructive behavior were found to have significantly ( $p = 0.042$  and  $p = 0.005$ , respectively) higher median AED loads (2.27, 95%CI 1.17–3.62 and 2.00, 95%CI 1.00–3.60, respectively) compared to those not exhibiting aggressive/destructive behavior (1.00, 95%CI 0.67–1.76 and 0.84, 95%CI 0.67–1.40, respectively).

The median AED loads of participants reporting antipsychotic medications and exhibiting SIB (1.00, 95%CI 0.70–1.57), aggressive/destructive (1.07, 95%CI 0.80–1.87) and stereotyped behavior

(1.09, 95%CI 0.67–1.66) (Supplementary Table 8) were not significantly different from those not exhibiting these behaviors (SIB 1.32, 95%CI 0.87–2.43; aggressive/destructive behavior 1.30, 95%CI 0.75–1.73; stereotyped behavior 1.30, 95%CI 0.87–2.43, respectively).

### 3.4. Factors associated with exhibiting SIB, aggressive/destructive, and stereotyped behavior

Binary logistic regression models (Table 3) demonstrated that having a severe/profound intellectual disability [OR 9.528 (95%CI: 1.904–47.681),  $p = 0.006$ ] was significantly associated with exhibiting SIB. Living in a residential/campus setting [OR 3.098 (95%CI: 1.267–7.577),  $p = 0.013$ ] and having a higher AED load [OR 1.298 (95%CI: 1.013–1.662),  $p = 0.039$ ] were significantly associated with exhibiting aggressive/destructive behavior after

**Table 2**  
Bivariate analysis of demographic & clinical factors among those with a report of an epilepsy diagnosis, taking a regular AED and exhibiting SIB ( $n = 141$ ), aggressive/destructive behavior ( $n = 137$ ), and stereotyped behavior ( $n = 141$ ).

Characteristic	Total SIB $n = 141$	Exhibit SIB $n = 52$	<i>P</i> value	Total aggressive/destructive behavior $n = 137$	Exhibit aggressive/destructive behavior $n = 54$	<i>P</i> value	Total stereotyped behavior $n = 141$	Exhibit stereotyped behavior $n = 71$	<i>P</i> value
<b>Gender</b>			0.379			0.333			0.049
Male	61 (43.3)	20 (38.5)		59 (43.1)	26 (48.1)		60 (42.6)	36 (50.7)	
Female	80 (56.7)	32 (61.5)		78 (56.9)	28 (51.9)		81 (57.4)	35 (49.3)	
<b>Age</b>			0.460			0.831			0.218
<50 years	16 (11.3)	8 (15.4)		15 (10.9)	7 (13.0)		16 (11.3)	11 (15.5)	
50–64 years	94 (66.7)	32 (61.5)		91 (66.4)	35 (64.8)		94 (66.7)	47 (66.2)	
65+ years	31 (22.0)	12 (23.1)		31 (22.6)	12 (22.2)		31 (22.0)	13 (18.3)	
<b>Level of intellectual disability</b>	$n = 133$	$n = 52$	<b>0.001*</b>	$n = 129$	$n = 52$	0.293	$n = 133$	$n = 67$	<b>&lt;0.001*</b>
Mild	21 (15.8)	2 (3.8)		21 (16.3)	6 (11.5)		21 (15.8)	3 (4.5)	
Moderate	54 (40.6)	18 (34.6)		53 (41.1)	20 (38.5)		53 (39.8)	24 (35.8)	
Severe/Profound	58 (43.6)	32 (61.5)		55 (42.6)	26 (50.0)		59 (44.4)	40 (59.7)	
<b>Place of residence</b>			0.025			0.025			0.003
Independent/Family/Community group home	55 (39.0)	14 (26.9)		54 (39.4)	15 (27.8)		55 (39.0)	19 (26.8)	
Residential/Campus	86 (61.0)	38 (73.1)		83 (60.6)	39 (72.2)		86 (61.0)	52 (73.2)	
<b>Cause of intellectual disability</b>	$n = 139$	$n = 51$	0.246	$n = 136$	$n = 53$	0.115	$n = 140$	$n = 71$	0.195
Down Syndrome	18 (12.9)	4 (7.8)		18 (13.2)	4 (7.5)		19 (13.6)	12 (16.9)	
Other etiology	37 (26.6)	12 (23.5)		37 (27.2)	12 (22.6)		38 (27.1)	15 (21.1)	
Unknown etiology	84 (60.4)	35 (68.6)		81 (59.6)	37 (69.8)		83 (59.3)	44 (62.0)	
<b>Type of seizures</b>			0.217			0.737			0.560
Generalized	80 (56.7)	26 (50.0)		76 (55.5)	29 (53.7)		80 (56.7)	42 (59.2)	
Other	61 (43.3)	26 (50.0)		61 (44.5)	25 (46.3)		61 (43.3)	29 (40.8)	
<b>Seizure frequency</b>	$n = 138$	$n = 51$	0.011	$n = 134$	$n = 52$	0.370	$n = 138$	$n = 70$	0.041
None in last year	78 (56.5)	36 (70.6)		76 (56.7)	32 (61.5)		79 (57.2)	46 (65.7)	
At least one in last year	60 (43.5)	15 (29.4)		58 (43.3)	20 (38.5)		59 (42.8)	24 (34.3)	
<b>Type of therapy</b>			0.217			0.819			0.267
Monotherapy	61 (43.3)	26 (50.0)		60 (43.8)	23 (42.6)		63 (44.7)	35 (49.3)	
Polytherapy	80 (56.7)	26 (50.0)		77 (56.2)	31 (57.4)		78 (55.3)	36 (50.7)	
<b>Median AED load (PDD/DDD) (95%CI)</b>	1.32 (1.00–1.57)	1.35 (0.95–1.66)	0.838 <sup>b</sup>	1.32 (1.00–1.57)	1.47 (1.00–2.13)	0.090 <sup>c</sup>	1.29 (1.00–1.50)	1.09 (0.70–1.57)	0.379 <sup>d</sup>
<b>Mood stabilizing AED</b>			1.000 <sup>a</sup>			0.601			0.368
Yes	128 (90.8)	47 (90.4)		124 (90.5)	48 (88.9)		128 (90.8)	66 (93.0)	
No	13 (9.2)	5 (9.6)		13 (9.5)	6 (11.1)		13 (9.2)	5 (7.0)	
<b>Comorbid mental health disorder</b>									
Psychotic disorder	11 (7.8)	4 (7.7)	1.000 <sup>a</sup>	11 (8.0)	4 (7.4)	1.000 <sup>a</sup>	11 (7.8)	6 (8.5)	0.772
Mood disorder	49 (34.8)	24 (46.2)	0.030	46 (33.6)	26 (48.1)	0.004	48 (34.0)	32 (45.1)	0.005
Anxiety disorder	49 (34.8)	24 (46.2)	0.030	46 (33.6)	24 (44.4)	0.030	49 (34.8)	31 (43.7)	0.025
<b>Co-prescribed psychotropic drugs</b>									
Antipsychotics	57 (40.4)	29 (55.8)	0.005	55 (40.1)	31 (57.4)	<b>0.001*</b>	57 (40.4)	38 (53.5)	<b>0.001*</b>
Antidepressants	46 (32.6)	17 (32.7)	0.989	44 (32.1)	24 (44.4)	0.013	45 (31.9)	20 (28.2)	0.337
Anxiolytics	25 (17.7)	11 (21.2)	0.416	24 (17.5)	15 (27.8)	0.011	25 (17.7)	16 (22.5)	0.132
Hypnotics & sedatives	19 (13.5)	10 (19.2)	0.126	19 (13.9)	9 (16.7)	0.445	19 (13.5)	11 (15.5)	0.480
Lithium	4 (2.8)	3 (5.8)	0.142 <sup>a</sup>	4 (2.9)	4 (7.4)	0.023 <sup>a</sup>	4 (2.8)	3 (4.2)	0.620 <sup>a</sup>
Drugs for dementia	4 (2.8)	1 (1.9)	1.000 <sup>a</sup>	4 (2.9)	2 (3.7)	0.647 <sup>a</sup>	4 (2.8)	2 (2.8)	1.000 <sup>a</sup>
Anti-cholinergic N04A	15 (10.6)	8 (15.4)	0.162	14 (10.2)	7 (13.0)	0.392	16 (11.3)	9 (12.7)	0.616

*P* value: Chi Square Test.

Statistically significant results (after applying Bonferroni correction) marked in bold and with an asterisk\*.

<sup>a</sup> Fisher Exact Test (2 sided). *P* value: for Chi Squared Test after applying Bonferroni correction  $\alpha = 0.05/20 = 0.0025$  thus  $p < 0.0025$  for significance.<sup>b</sup> Mann–Whitney *U* Test: Exhibit mean rank = 69.39 ( $n = 51$ ), do not exhibit mean rank = 67.96 ( $n = 85$ ). Do not exhibit SIB median AED load: 1.30 (95%CI 0.80–1.87).<sup>c</sup> Aggressive/Destructive Behavior Mann–Whitney *U* Test: Exhibit mean rank = 73.62 ( $n = 51$ ), do not exhibit mean rank = 62.02 ( $n = 81$ ). Do not exhibit aggressive/destructive behavior median AED load 1.11 (95%CI 0.80–1.57).<sup>d</sup> Stereotyped Behavior Mann–Whitney *U* Test: Exhibit mean rank = 65.53 ( $n = 68$ ), do not exhibit mean rank = 71.47 ( $n = 68$ ). Do not exhibit stereotyped behavior median AED load 1.30 (95%CI 1.00–2.25).

**Table 3**  
Binary logistic regression of factors associated with exhibiting SIB, aggressive/destructive and stereotyped behavior among older people with intellectual disability.

Characteristic	Self-Injurious Behavior (SIB)		Aggressive/Destructive Behavior		Stereotyped Behavior	
	<i>n</i> = 129 Odds Ratio (95%CI)	<i>P</i> Value	<i>n</i> = 125 Odds Ratio (95%CI)	<i>P</i> Value	<i>n</i> = 129 Odds Ratio (95%CI)	<i>P</i> Value
<b>Age</b>						
<50 years	1 (Reference)		1 (Reference)		1 (Reference)	
50–64 years	0.659 (0.195–2.231)	0.503	0.592 (0.154–2.277)	0.446	0.341 (0.086–1.343)	0.124
65+ years	0.813 (0.199–3.324)	0.773	0.969 (0.218–4.313)	0.967	0.220 (0.047–1.035)	0.055
<b>Level of intellectual disability</b>						
Mild	1 (Reference)		1 (Reference)		1 (Reference)	
Moderate	4.018 (0.818–19.741)	0.087	0.969 (0.294–3.192)	0.959	4.281 (1.060–17.294)	<b>0.041*</b>
Severe/Profound	9.528 (1.904–47.681)	<b>0.006*</b>	1.098 (0.320–3.760)	0.882	8.113 (1.969–33.430)	<b>0.004*</b>
<b>Type of residence</b>						
Family/Independent/Community Group Home	1 (Reference)		1 (Reference)		1 (Reference)	
Residential/Campus	1.403 (0.591–3.331)	0.442	3.098 (1.267–7.577)	<b>0.013*</b>	2.897 (1.214–6.911)	<b>0.017*</b>
<b>AED load</b>	0.952 (0.749–1.209)	0.686	1.298 (1.013–1.662)	<b>0.039*</b>	0.915 (0.714–1.173)	0.484

Reference groups – <50 years, mild intellectual disability, family/independent/community group home.

Statistically significant results marked in bold and with an asterisk\*.

SIB: Reference category: Does not exhibit SIB.

Cox & Snell *R*<sup>2</sup> 0.125, Nagelkerke *R*<sup>2</sup> 0.170.

Aggressive/Destructive Behavior: Reference category: Does not exhibit aggressive/destructive behavior.

Cox & Snell *R*<sup>2</sup> 0.099, Nagelkerke *R*<sup>2</sup> 0.134.

Stereotyped Behavior: Reference category: Does not exhibit stereotyped behavior.

Cox & Snell *R*<sup>2</sup> 0.191, Nagelkerke *R*<sup>2</sup> 0.255.

adjusting for confounders. Having a moderate [OR 4.281 (95% CI: 1.060–17.294), *p* = 0.041] or severe/profound intellectual disability [OR 8.113 (95% CI: 1.969–33.430), *p* = 0.004], and living in a residential/campus setting [OR 2.897 (95% CI: 1.214–6.911), *p* = 0.017] were associated with exhibiting stereotyped behavior. Age was not found to be associated with exhibiting SIB, aggressive/destructive behavior, or stereotyped behavior (Table 3).

#### 4. Discussion

##### 4.1. Main findings

To our knowledge, this is the first study examining AED load (PDD/DDD) and challenging behaviors in older adults with intellectual disability and a diagnosis of epilepsy. Almost two-thirds of participants with epilepsy and available information reported exhibiting challenging behaviors with an increased prevalence among those with greater severity of intellectual disability. Aggressive/destructive and stereotyped behaviors were associated with living in residential/campus settings, adjusting for confounders. Over half of participants exhibiting challenging behaviors reported taking AED polytherapy. The highest median AED load was found in participants exhibiting aggressive/destructive behavior. Participants with a severe/profound intellectual disability exhibiting SIB and aggressive/destructive behavior had significantly higher median AED loads compared to participants not exhibiting these behaviors. Higher AED load was associated with exhibiting aggressive/destructive behavior after adjusting for confounders.

##### 4.2. Comparison with other studies

Many AEDs have been associated with adverse behavioral effects in people with epilepsy, although there is little evidence from randomized controlled trials [38,39]. A report examining behavioral disorder in people with intellectual disability and epilepsy concluded that AEDs may provoke either positive or negative behavioral side effects in people with intellectual disability [12]. Antiepileptic drug polytherapy has also been associated with drug-related behavioral problems like irritability and aggressive

behavior [40,41]. In this study, we did not find a significant association between AED use (monotherapy or polytherapy) and reporting challenging behaviors. A higher prevalence of challenging behaviors has been found in some studies of people with intellectual disability and epilepsy who take AED polytherapy [9,42]. However, a meta-analysis examining this association did not find a definite correlation between the rate of challenging behaviors and polytherapy with AED medications [9].

Increased levels of refractory epilepsy [43] in this population group often necessitate use of high AED doses and polytherapy, thus contributing to higher AED loads [44] and increasing the risk of adverse effects [45]. We found higher median AED loads (PDD/DDD) were associated with exhibiting both SIB and aggressive/destructive behavior among specific subgroups when comparing demographic and clinical characteristics. While high AED doses and polytherapy might be expected among participants reporting increased seizure frequency, we also found that a higher median AED load in this subgroup was associated only with participants exhibiting aggressive/destructive behavior. Significantly higher median AED loads were also found in participants taking AED monotherapy and exhibiting SIB compared to not exhibiting SIB, requiring caution in all therapy regimens. Taking antipsychotics or antidepressants was not associated with a higher median AED load across all behavior types.

Furthermore, in participants with the most severe intellectual disability, where the greatest prevalence of challenging behaviors were found (56.5%), significantly higher median AED loads were found among participants exhibiting both SIB and aggressive/destructive behavior compared to participants with severe/profound intellectual disability not exhibiting these behaviors (SIB and aggressive/destructive behavior, respectively) indicating a higher AED load (PDD/DDD) may be an increased risk for some behavioral problems in people with greater severity of intellectual disability. The overall median AED load for participants exhibiting challenging behavior was found to be lower than for participants not exhibiting challenging behavior due to lower AED loads for stereotyped behavior.

We did not find any study allowing direct comparisons of AED load (PDD/DDD) and challenging behavior, either in people with intellectual disability or in the general population. Mood stabiliz-



ing AEDs were widely prescribed to participants exhibiting challenging behaviors in this study, but they are recognized first line treatments for many seizure types. It is plausible that the mood stabilizing properties of some AEDs were exploited and the association between AED load and some behaviors may occur as the presence of behaviors prompts a response, and one response is to prescribe. However, although a systematic review found behavioral improvement with the use of some antiepileptic medication [46], this was in 2008, and there is still little high quality evidence to support their use.

Therefore, our findings pose the question of whether the presence of challenging behaviors in people with epilepsy and intellectual disability leads to greater prescribing of some AEDs for their mood stabilizing properties, thus contributing to higher AED loads; or if the dosages of AED medication required to treat refractory seizures produces high AED loads, leading to greater levels of challenging behaviors. Polytherapy and high AED dosages have also been found to be associated with numerous comorbidities including poor bone health [47], fracture risk [48], and adverse cognitive effects [49] necessitating greater caution.

#### 4.3. Implications for practice

Numerous factors can impact on behavioral outcomes, including the level of intellectual disability [50], AED type [11], dosage [51], titration speed [51], epilepsy diagnosis [18], polytherapy [42,51,52], previous psychiatric illness [53], and individual patient tolerability [11,54], therefore making it difficult to determine those that are associated and the nature of the association. Identifying possible adverse effects of AEDs (which may present as challenging behaviors) in people with intellectual disability is a substantial challenge, due in part to limited verbal and communication skills [55–57], particularly in people with severe/profound intellectual disability, those who are probably most at risk [8]. To add to the complexity, high levels of psychotropic prescribing are found in people with intellectual disability, often to treat behavioral rather than psychiatric problems [58] leading to an increased likelihood of drug–drug interactions with AEDs and adverse effects, meriting increased vigilance for breakthrough behavioral problems and avoidance of high dosages.

Residential/campus settings are most strongly associated with these issues, necessitating the provision of long-term care that is complex, burdensome, and resource intensive. In this study, residential/campus settings were the most common type of residence for people exhibiting challenging behaviors (70.8%), and were associated with exhibiting both aggressive/destructive and stereotyped behaviors. Moreover, as people with intellectual disability living in community-based settings get older, their care needs grow in complexity. For those with a diagnosis of epilepsy, regular and comprehensive assessment of their needs is warranted to enable them to live in a type of setting that protects both them and others, yet offering them the greatest amount of freedom.

#### 4.4. Strengths of study

Our study used a large, nationally representative sample of older Irish adults with intellectual disability and representative of the older population of people with intellectual disability in Ireland. Detailed medication data for 90.1% of Wave 3 participants were obtained which was confirmed by interviewers at the time of the interview. The design of the medication record allowed for high quality acquisition of medication data. All participants and/or their proxies received the PIQ which contained the medication record/challenging behaviors section one week prior to the face-to-face interview giving them an opportunity to consult the participants' medication/health records. A stringent VIF cutoff threshold

(<2) was employed to rule out multicollinearity between variables in the regression analysis, contributing to the strength of the study.

#### 4.5. Limitations of study

Data were not available concerning medications for 19 participants, for 32 participants regarding challenging behaviors, and regarding AED load for six participants, therefore, our sample was under-powered to evaluate small sub-groups. As a result, associations found in this study are based on small group sizes. Liver and/or renal function was not taken into consideration for AED load PDD/DDD ratio. We found low numbers of participants reporting focal seizures, which necessitated grouping focal with unknown seizures. Due to the observational cross-sectional study design, we can only describe associations between challenging behaviors and demographic and clinical factors. This study was not randomized to match the activities of AEDs in relation to challenging behaviors with controls. In our multivariate analysis, any probable bias was removed where possible by adjusting for confounders. Nevertheless, residual confounding factors may remain. Additionally, due to small sample sizes for our binary logistic regression, we were limited to examining four predictors.

## 5. Conclusion

Our findings suggest that challenging behaviors are a considerable problem for older people with intellectual disability and a diagnosis of epilepsy. Significantly higher median AED loads were found in some subgroups, including those with severe/profound intellectual disability who exhibit SIB and aggressive/destructive behavior, raising the question as to whether AED load is a precipitating factor or a consequence in these people. However, a large number of possible contributory and interacting factors exist, thus larger, better powered studies are needed to discern if AED load contributes to behavioral problems in sub groups with different seizure types, and to enable different causal factors to be assessed. In addition, more discriminatory and easy to use tools are required to enable regular comprehensive reviews to be performed, considering (1) the epilepsy and its impact; (2) the behaviors and potential associated factors; (3) the AED(s) used to treat epilepsy; (4) any AED(s) used for behavioral problems; and (5) any psychotropic drugs prescribed, particularly those without a clear indication.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgments

The authors of this study would like to express their thanks to the people with intellectual disability, their families, carers, the services concerned, the IDS-TILDA International Scientific Advisory Committee and the Intellectual Disability Consultative Groups for their support. We would like to greatly acknowledge the contributions of Dr. Rachael Carroll. The IDS-TILDA study is funded by the Department of Health in Ireland and the Health Research Board. The lead author (RM) received funding for a PhD from a Trinity College Dublin Studentship. The funding body did not play a role in the study design or writing of the article. The views expressed are those of the authors and are not necessarily those of the Department of Health, the Health Research Board or Trinity College Dublin.

## Declarations of Interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2021.108191>.

## References

- Helmstaedter C, Aldenkamp AP, Baker GA, Mazarati A, Ryvlin P, Sankar R. Disentangling the relationship between epilepsy and its behavioral comorbidities - the need for prospective studies in new-onset epilepsies. *Epilepsy Behav* 2014;31:43–7.
- van Ool JS, Snoeijen-Schouwenaars FM, Schelhaas HJ, Tan IY, Aldenkamp AP, Hendriksen JGM. A systematic review of neuropsychiatric comorbidities in patients with both epilepsy and intellectual disability. *Epilepsy Behav* 2016;60:130–7.
- O'Dwyer C, McCallion P, Burke É, Carroll R, O'Dwyer M, McCarron M. Prevalence and associated factors of problem behaviours among older adults with intellectual disabilities in Ireland. *Res Dev Disabil* 2018;80:192–204.
- Lowe K, Allen D, Jones E, Brophy S, Moore K, James W. Challenging behaviours: prevalence and topographies. *J Intellect Disabil Res* 2007;51:625–36.
- Blickwedel J, Ali A, Hassiotis A. Epilepsy and challenging behaviour in adults with intellectual disability: A systematic review. *J Intellect Dev Disabil* 2019;44:219–31.
- Ali A, Blickwedel J, Hassiotis A. Interventions for challenging behaviour in intellectual disability. *Adv Psychiatr Treat* 2014;20:184–92.
- Smith KRM, Matson JL. Behavior problems: differences among intellectually disabled adults with co-morbid autism spectrum disorders and epilepsy. *Res Dev Disabil* 2010;31:1062–9.
- McClintock K, Hall S, Oliver C. Risk markers associated with challenging behaviours in people with intellectual disabilities: a meta-analytic study. *J Intellect Disabil Res* 2003;47:405–16.
- Deb S, Akrouf Brizard B, Limbu B. Association between epilepsy and challenging behaviour in adults with intellectual disabilities: systematic review and meta-analysis. *BJPsych Open* 2020;6:e114.
- de Winter CF, Jansen AA, Evenhuis HM. Physical conditions and challenging behaviour in people with intellectual disability: a systematic review. *J Intellect Disabil Res* 2011;55:675–98.
- Schmitz B. Effects of antiepileptic drugs on mood and behavior. *Epilepsia* 2006;47:28–33.
- Kerr M, Linehan C, Brandt C, Kanemoto K, Kawasaki J, Sugai K, et al. Behavioral disorder in people with an intellectual disability and epilepsy: A report of the Intellectual Disability Task Force of the Neuropsychiatric Commission of ILAE. *Epilepsia Open* 2016;1:102–11.
- Perucca P, Mula M. Antiepileptic drug effects on mood and behavior: molecular targets. *Epilepsy Behav* 2013;26:440–9.
- Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. *Drug Saf* 2007;30:555–67.
- Leunissen CLF, de la Parra NM, Tan IY, Rentmeester TW, Vader CI, Veendrick-Meekes MJ, et al. Antiepileptic drugs with mood stabilizing properties and their relation with psychotropic drug use in institutionalized epilepsy patients with intellectual disability. *Res Dev Disabil* 2011;32:2660–8.
- Nadkarni S, Devinsky O. Psychotropic effects of antiepileptic drugs. *Epilepsy Curr* 2005;5:176–81.
- Beran RG, Gibson RJ. Aggressive behaviour in intellectually challenged patients with epilepsy treated with lamotrigine. *Epilepsia* 1998;39:280–2.
- Cramer JA, De Rue K, Devinsky O, Edrich P, Trimble MR. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. *Epilepsy Behav* 2003;4:124–32.
- Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Drug load in clinical trials: a neglected factor. *Clin Pharmacol Ther* 1997;62:592–5.
- Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. *Epilepsia* 1997;38:570–5.
- Watkins LV, Pickrell WO, Kerr MP. Treatment of psychiatric comorbidities in patients with epilepsy and intellectual disabilities: Is there a role for the neurologist? *Epilepsy Behav* 2019;98:322–7.
- Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 2011;52: 2133–8.
- Kerr M, Scheepers M, Arvio M, Beavis J, Brandt C, Brown S, et al. Consensus guidelines into the management of epilepsy in adults with an intellectual disability. *J Intellect Disabil Res* 2009;53: 687–94.
- McCarron M, O'Dwyer M, Burke E, McGlinchey E, McCallion P. Epidemiology of epilepsy in older adults with an intellectual disability in Ireland: associations and service implications. *Am J Intellect Dev Disabil* 2014;119:253–60.
- McCarron M, Swinburne J, Burke E, McGlinchey E, Mulryan N, Andrews V, Foran S, McCallion P. Growing older with an intellectual disability in Ireland 2011: First results from the intellectual disability supplement to the Irish Longitudinal Study on Ageing. Dublin: School of Nursing & Midwifery, Trinity College; 2011. Available from <https://www.tcd.ie/tcaid/assets/pdf/istildareport2011.pdf>.
- WHO. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. World Health Organisation; 1992.
- IDS-TILDA. Health, wellbeing, and social inclusion: ageing with an intellectual disability in Ireland. Evidence from the first ten years of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA). Trinity College Dublin. 2017. Available from <https://www.tcd.ie/tcaid/assets/pdf/wave3report.pdf>.
- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12:1500–24.
- Monaghan R, O'Dwyer M, Luus R, Mulryan N, McCallion P, McCarron M, et al. Antiepileptic drugs, occurrence of seizures and effect of co-administration of potential seizure threshold-lowering psychotropic drugs in adults with intellectual disability who have epilepsy. *J Appl Res Intellect Disabil* 2021;34:818–29.
- O'Dwyer M, Peklar J, McCallion P, McCarron M, Henman MC. Factors associated with polypharmacy and excessive polypharmacy in older people with intellectual disability differ from the general population: a cross-sectional observational nationwide study. *BMJ Open* 2016;6:e010505.
- SmPC (Midazolam). Buccolam (Midazolam) UK and Ireland. Shire, Available from <https://www.medicines.ie/medicines/buccolam-2-5mg-5mg-7-5mg-and-10mg-ozomucosal-solution-31492/smpc>, Accessed 22nd August 2019.
- Deckers CLP, Hekster YA, Keyser A, Van Lier HJJ, Meinardi H, Renier WO. Monotherapy versus polytherapy for epilepsy: a multicenter double-blind randomized study. *Epilepsia* 2001;42:1387–94.
- Rojahn J, Rowe EW, Sharber AC, Hastings R, Matson JL, Didden R, Kroes DBH, Dumont ELM. The Behavior Problems Inventory-Short Form for individuals with intellectual disabilities: Part I: development and provisional clinical reference data. *J Intellect Disabil Res* 2012;56: 527–545.
- Mascitelli AN, Rojahn J, Nicolaides VC, Moore L, Hastings RP, Christian-Jones C. The Behaviour Problems Inventory-Short Form: reliability and factorial validity in adults with intellectual disabilities. *J Appl Res Intellect Disabil* 2015;28:561–71.
- International League Against Epilepsy (ILAE). Classification of the Epilepsies. 2017. Available from <https://www.ilae.org/guidelines/definition-and-classification/ilae-classification-of-the-epilepsies-2017>, Accessed 20th September 2020.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 1995;57:289–300.
- Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373–9.
- Kerr MP. Behavioral assessment in mentally retarded and developmentally disabled patients with epilepsy. *Epilepsy Behav* 2002;3:14–7.
- Working group of the International Association of the Scientific Study of Intellectual Disability. Clinical guidelines for the management of epilepsy in adults with an intellectual disability. *Seizure* 2001;10: 401–409.
- Devinsky O. Psychiatric comorbidity in patients with epilepsy: implications for diagnosis and treatment. *Epilepsy Behav* 2003;4(Suppl 4):S2–S10.
- Schmitz B. Psychiatric syndromes related to antiepileptic drugs. *Epilepsia* 1999;40:s65–70.
- Espie CA, Gillies JB, Montgomery JM. Antiepileptic polypharmacy, psychosocial behaviour and locus of control orientation among mentally handicapped adults living in the community. *J Intellect Disabil Res* 1990;34: 351–360.
- Forsgren L, Edvinsson S-O, K:son Blomquist H, Heijbel J, Sidenvall R. Epilepsy in a population of mentally retarded children and adults. *Epilepsy Res* 1990;6:234–48.
- Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, Muscas G, La Neve A, Striano P, Perucca E, Group SS. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. *Epilepsia* 2010;51: 797–804.
- Schmidt D, Elger C, Holmes GL. Pharmacological overtreatment in epilepsy: mechanisms and management. *Epilepsy Res* 2002;52:3–14.
- Deb S, Chaplin R, Sohanpal S, Unwin G, Soni R, Lenore L. The effectiveness of mood stabilizers and antiepileptic medication for the management of behaviour problems in adults with intellectual disability: a systematic review. *J Intellect Disabil Res* 2008;52:107–13.
- Burke EA, McCallion P, Carroll R, Walsh JB, McCarron M. An exploration of the bone health of older adults with an intellectual disability in Ireland. *J Intellect Disabil Res* 2017;61:99–114.
- Shen C, Chen F, Zhang Y, Guo Y, Ding M. Association between use of antiepileptic drugs and fracture risk: a systematic review and meta-analysis. *Bone* 2014;64:246–53.
- Loring DW, Meador KJ. Cognitive and behavioral effects of epilepsy treatment. *Epilepsia* 2001;42(Suppl 8):24–32.
- Espie CA, Watkins J, Curtice L, Espie A, Duncan R, Ryan JA, et al. Psychopathology in people with epilepsy and intellectual disability; an

- investigation of potential explanatory variables. *J Neurol Neurosurg Psychiatry* 2003;74:1485–92.
- [51] Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. *J Clin Psychopharmacol* 2012;32:362–75.
- [52] Espie CA, Pashley AS, Bonham KG, Sourindhrin I, O'Donovan M. The mentally handicapped person with epilepsy: a comparative study investigating psychosocial functioning. *J Intellect Disabil Res* 1989;33: 123–135.
- [53] Kanner AM, Wu J, Faught E, Tatum WO, Fix A, French JA. A past psychiatric history may be a risk factor for topiramate-related psychiatric and cognitive adverse events. *Epilepsy Behav* 2003;4:548–52.
- [54] Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. *Epilepsia* 1995;36:546–65.
- [55] Mula M, Monaco F. Antiepileptic drugs and psychopathology of epilepsy: an update. *Epileptic Disord* 2009;11:1–9.
- [56] Doran Z, Shankar R, Keezer MR, Dale C, McLean B, Kerr MP, et al. Managing anti-epileptic drug treatment in adult patients with intellectual disability: a serious conundrum. *Eur J Neurol* 2016;23:1152–7.
- [57] Watkins L, O'Dwyer M, Kerr M, Scheepers M, Courtenay K, Shankar R. Quality improvement in the management of people with epilepsy and intellectual disability: the development of clinical guidance. *Expert Opin Pharmacother* 2020;21:173–81.
- [58] Sheehan R, Hassiotis A, Walters K, Osborn D, Strydom A, Horsfall L. Mental illness, challenging behaviour, and psychotropic drug prescribing in people with intellectual disability: UK population based cohort study. *BMJ* 2015;351: h4326.