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Efficacy and tolerability of Brivaracetam in people with intellectual disability compared to those without intellectual disability

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Efficacy and tolerability of Brivaracetam in people with intellectual disability compared to those without intellectual disability

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A B S T R A C T

Introduction: In England, nearly a quarter of people with intellectual disability (PwID) have epilepsy. Though 70 % of PwID have pharmaco-resistant seizures only 10 % are prescribed anti-seizure medication (ASMs) licenced for pharmaco-resistance. Brivaracetam (BRV) licenced in 2016 has had nine post-marketing studies involving PwID. These studies are limited either by lack of controls or not looking at outcomes based on differing levels of ID severity. This study looks at evidence comparing effectiveness and side-effects in PwID to those without ID prescribed Brivaracetam (BRV).
Methods: Pooled case note data for patients prescribed BRV (2016–2022) at 12 UK NHS Trusts were analysed. Demographics, starting and maximum dose, side-effects, dropouts and seizure frequency between ID (mild vs. moderate-profound (M/P)) and general population for a 12-month period were compared. Descriptive analysis, Mann-Whitney, Fisher's exact and logistic regression methods were employed.
Results: 37 PwID (mild 17 M/P 20) were compared to 102 without ID. Mean start and maximum dose was lower for PwID than non-ID. Mean maximum dose reduced slightly with ID severity. No difference was found between ID and non-ID or between ID groups (Mild vs M/P) in BRV's efficacy i.e. >50 % seizure reduction or tolerability. Mental and behavioural side-effects were more prevalent for PwID (27.0 % ID, 17.6 % no ID) but not significantly higher ($P = 0.441$) or associated with ID severity ($p = 0.255$).
Conclusion: This is the first study on BRV, which compares ID cohorts with differing severity and non-ID. Efficacy, tolerability and side-effects reported are similar across differing ID severity to those with no ID.

1. Introduction

Epilepsy poses a substantial burden to people with Intellectual Disability (PwID) in England. Present in around 22 % [1], it was the second most common cause of avoidable death in 2022, eclipsed only by COVID-19 [2]. Prevalence of epilepsy is robustly associated with the severity of ID, with as many as half of individuals with profound ID diagnosed [1]. Levels of mental and physical health comorbidity for PwID result in complex and nuanced presentations which can be highly challenging for clinicians looking to manage an individual's epilepsy [3,4]. Added to this is the lack of holistic expertise to manage this vulnerable population's complex needs [5,6,7].

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1.1. Newer antiseizure medication (ASM) and PwID

It is considered that nearly 70 % of PwID are pharmaco-resistant but only 10 % are on newer Anti-Seizure Medications (ASMs) licenced for pharmaco-resistant epilepsy [8,9,10]. Polypharmacy is also more prevalent and increases with ID severity, creating a context within which concerns regarding interactivity, tolerability, and efficacy add to the complexity. [11] High levels of treatment resistance and increased vulnerability to cognitive-behavioural side effects add to this complex clinical picture [12]; [11,4] Guidance on prescribing for this complex

Table 1
BRV Studies in PwID compared.

	Andres et al 2018	Lafortune et al 2020	Theochari et al 2019	Foo et al 2019	Villanueva et al 2019	Adewusi et al 2020	Gillis et al 2020	Green et al 2022	Naddell et al 2023	UK Ep-ID Register
Country	Germany single site institution	Single site Canada	Single tertiary centre UK	Single tertiary centre UK	18 centres Spain	11 centres, UK	single site institution Netherlands	Single tertiary centre	Single tertiary centre, UK	13 centres UK
Study design	Retrospective Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospect Cohort	Retrospective Cohort
Participant **ID Diagnosis**	ID, ID levels diagnosis criteria ICD 10	No ID & ID No formal diagnosis criteria	No ID & ID No formal diagnosis criteria	No ID & ID No formal diagnosis criteria	No ID& ID No formal diagnosis criteria	No ID & ID No formal diagnosis criteria	ID, ID Levels diagnosis criteria ICD 10	No ID & ID No formal diagnosis criteria	No & ID No formal diagnosis criteria	No ID, ID Levels diagnosis criteria ICD 10
Study pop.	33 Mild 13 (40%) M/P 20(60%)	14/38 (37%)	3/25 (12%)	41/134 (30.5%)	182/570 (31.9%)	58/290 (20%)	116 Border -20.7 Mild 37.1 Mod 12.9% Severe 19.8% Prof 9.5%	63/200 (31.5%)	15/109 (13.8%)	37/139 (26.6%) Mild 17 (12.2%; 46%) M/P 20 (14.4%; 54%)
Efficacy >50% **12 Month unless stated**	Mild n3 23.% M/P n6 30 % (6 months) 19% (all) at 12 months	41.2%	40% (8 months)	37% vs. 32% (NS)	32.2% Vs 43.4% (S)	15.5% Vs. 21.7% (S)	>50% not reported.	20.5% Vs. 26% (NS)	30.8%	32.4% Vs. 33.7% (NS) Mild n6 35.3% M/P n6 30%
ID level analysis	Yes	No	No	No	No	No	Yes	No	No	Yes
Retention (1 year)	37.5% (all patients) 12 months	59.2%	N/A	66% vs. 62% (NS) 26 months	93.4% vs 90.2% (3 months) 70.4%	68.9% vs. 68.7% (NS)	58.1% (all) 6 months: 78.3% n54 Border–moderate. 68.0% n17 Severe-Prof (NS)	72%	70%	78.4% v 73.0% (NS) 76.5% n13 – mild ID 80.0% n16 – M/P
Mean, Median MAX dose	200 mgs responders (mean) 171 mgs - non-responders (mean)	144 mgs overall 117 mgs mgs non-responders (mean)	150 mgs (median)	200 mgs (median)	NA	ID 25 mgs (median) Non-ID 150 mgs (median)	88.1 mgs (mean)	NA	146.4 mgs	152 mg non-ID (mean) 150 mg M-ID (Mean) 137 mg M/P ID (mean)
Mental health **&** **behaviour**	39% Aggression 27%	35.7% ID vs 29.2% N-ID (NS)	Not specific Depression& aggression 20%	Aggression 17% Vs 26% Depression 12%	Not specific general side effects 32.4% ID Vs. 43% N-ID (S)	Not specific general side effects 58.6% ID vs. 31.5% N-ID (NS)	30% behaviour issues	ID a risk factor (S)	Anger 40% (S),	27.0% Vs 17.6% (NS) No differences between ID groups

and vulnerable population remains cautious and primarily drawn from that recommended from the general population, coupled with advice for closer monitoring [11].

Pre-market studies pertaining to the efficacy and tolerability of ASMs still rarely include PwID. [11], [13] When included, there is little evaluation of the level and nature of ID and its associated co-morbidities [14,7].

Evidence from post-trial observation data, whose value has been increasing recognised [15] have provided greater awareness around tolerability, efficacy and side-effects of various ASMs for PwID [16]. Data regarding response and ID severity, is often however absent from studies, despite recognition of differing comorbidities, complex clinical features and potential for varying treatment resistance and response in this population [12]. This includes third generation ASMs, such as Brivaracetam (BRV), with observational research data continuing to focus primarily on PwID without providing insights into their severity and associated co-morbidities.

1.2. BRV and PwID

BRV was granted European Medicines Agency (EMA) authorisation for use within Europe and the UK in January 2016 [17]. Nine post-license studies have provided observational data regarding the efficacy and tolerability of BRV in PwID. Details of these studies are provided in Table 1. Early research were small scale single site retrospective cohort studies conducted in Germany [18], Canada [19], and the UK [20], along with a separate larger single site UK study [21]. With the exception of the German study, all data focussed on comparison between PwID and those with epilepsy and no ID. These initial studies identified that BRV constitutes a similarly efficacious and tolerable ASM for PwID, with the larger UK single-site study (ID n41, no ID n124) reporting no significant differences in efficacy and retention [21]. Reported side-effects were also similar across ID and no ID populations, but the German data did raise concerns regarding tolerability, with side-effect (particularly increases of aggressive behaviour) and limited efficacy resulting in only 37 % of this cohort still taking BRV at 12 months [18].

The first multi-site (18 centre) study of BRV was conducted in Spain and reported data from 570 people, 182 of whom were PwID [22]. Retention rates here were 70.4 % at 12 months (not reported for specific groups), but BRV was shown to be less efficacious in PwID; with significantly fewer seeing a '>50 % reduction' in reported seizure activity (32.2 % ID, 43.4 % no ID; $p = 0.011$). Less PwID did however experience adverse events, compared to those with no ID (32.4 % ID, 43.3 % no ID; $P = 0.013$). The authors conclusions that BRV is largely well tolerated and reasonably efficacious in PwID, has been further supported by four studies published more recently [23,24,25,26].

The largest of the four additional studies was conducted across 11 sites in the UK, reporting data from 58 PwID and 290 with no ID [23]. BRV retention rates (68 % for both groups at 12 months) but a significantly better efficacy (>50 % seizure reduction) for no ID patients were reported (21.7 % ID, 15.5 % no ID; $p = 0.009$). Although not significant, ($p = 0.245$) adverse effects were more prevalent in those with ID (31.5 % ID, 58.6 % no ID). The additional smaller single site studies did not report any significant variation in retention or efficacy, but did also highlight side effects, with ID identified as a significant risk factor for mental health/behavioural side effects ($p = 0.004$) in one study [25] and associated with an elevated rate of anger when compared to those with no ID (40 % vs 14.9 %) in a separate study [26].

Despite this largely encouraging evidence base, further data is arguably required to help build prescribing confidence and guidance of BRV for PwID. In addition, data for those with varying severity of ID is largely absent from the current research evidence detailed above. Of the nine studies discussed, only two included ID severity of participants [18,24] Both studies, were conducted at single-sites, one in Germany with small (n33) numbers [18] and the other in the Netherlands, with significantly larger numbers (n116) but limited reporting of comparative data [24]. Neither study included a comparator of general population (non-ID) patients. There is therefore no study to date which has investigated the efficacy and tolerability of BRV in PwID according to the severity of their ID, with a comparative non-ID cohort.

Here we report on a new arm of a feasibility tested and well-established Epilepsy Research Database Register for PwID and epilepsy, (referred to as the Ep-ID Register in this paper and detailed below) [27,28,29] looking to compare response to BRV for cohorts of PwID with differing severity and a cohort of people with no ID.

2. Methodology

This was a multi-center retrospective evaluation of treatment with data collected from 12 centers in England UK. The STROBE Checklist for case-control studies was used to report the findings (supplementary information 1).

The data presented in this paper is from one arm of the Cornwall Ep-ID Register, a UK NHS based Research Database Register for people with epilepsy who have an ID. Ep-ID uses an NHS ethically approved (14/SC/1270) and UK National Institute of Health Research portfolio (NIHR 31484) research methodology, applying a systematic and standardised non-interventional observational method for collecting and measuring outcomes of licensed epilepsy treatments. Retrospective data for PwID and epilepsy and people from the general population (defined as 'no ID') who have epilepsy is collected from patient medical records across participating UK NHS Trusts and compared. Study data for this Ep-ID arm (BRV), were collected at 12 collaborating NHS Trusts from across England, who acted as Data Collection Centres (DCCs). DCCs followed the standardised Ep-ID protocol used on previous studies of post 2004 ASMs [27,28,29]. Crucially the Ep-ID Register collects specific data offering the opportunity to compare people with different severity of ID. The justification and rationale for dividing PwID into "mild" and moderate to profound" ID is provided in appendix A. This was also used as guidance to help differentiate the two groups when going through their records.

2.1. Eligibility and consent

All NHS patients aged 18 or over who were currently or previously prescribed BRV at participating English NHS Trusts i.e. DCCs, were eligible to participate. The study was open to recruitment from July 2020 until December 2022. All those recruited had 12 months of BRV data recorded in patient records before December 2022. Potential participants were approached either by letter and participant information documents and telephone communication requesting return of consent forms or introduced to the study during face-to-face routine clinics. PwID were provided with 'Easy Read' information sheets and consent forms. Where the individual lacked capacity to consent, next of kin and/or carers were approached to consent on their behalf.

2.2. Data collection and categorisation

Pre-existing and routine clinical data recorded in NHS patient medical records were collected by researchers at the sponsor site and DCCs applying the standardised Ep-ID data collection process. Support and informal training were provided as appropriate. Data collection focussed on demographics and clinical features related to epilepsy, ID and severity and comorbidities. PwID were categorised as 'mild' or 'moderate-profound' following ICD-10 classifications [30]. Data related to BRV and concomitant ASMs were collected for a fifteen-month period (three-month period prior to commencement of BRV and twelve months post first prescription), with dose and seizure frequency collected at five time points. Withdrawal within twelve months and reason for withdrawal, were identified and recorded. Efficacy (seizure impact) at 12 months was categorised into "At least 50 % improvement" and "No improvement/less than 50 % improvement". This was calculated using

frequency and intensity of seizures, or where verbatim recording of percentage changes in seizures were documented. Common side-effects in the UK British National Formulary (BNF) along with any uncommon side-effects were also collected.

People approached were first prescribed BRV between March 2016 and September 2021, for a subsequent 12-month period. Data were pseudonymised locally at DCCs and transferred securely to the sponsor site in a standardised, password-protected format. Data collected were standardised to account for any inconsistences with data queries raised with DCCs where appropriate.

2.3. Analysis

Baseline data were summarised by the median and interquartile range (IQR) for continuous data, and the number and percentage for categorical data. Fisher's exact test was used to test for univariable associations between ID group (general population/mild ID/moderate to profound ID) and the categorical baseline characteristics. A similar approach was used to test for univariable associations between ID group and the study outcomes (withdrawal, efficacy, adverse events). Differences in withdrawal, efficacy and risk of side-effects between no ID and ID groups were further explored using logistic regression analysis. Potential sources of confounding bias were addressed through adjustment of regression models for demographic factors and baseline health conditions. In the primary analysis, differences between ID groups were reported as odds ratios estimated from logistic regression models with adjustment for age and gender. The threshold for statistical significance was $p = 0.05$. A complete cases approach was used to handling missing data. All analyses were performed using the R environment for statistical computing. Although the study was adequately powered to detect large effect sizes, it was underpowered to detect small to moderate effect sizes.

3. Results

3.1. Participants and dropouts

A total of 139 patients were recruited as research participants for this arm of the Ep-ID Research Database Register from across 12 UK NHS Trusts. Of these 37 enrolled participants (26.6 %) had an ID diagnosis, 17 with mild (12.2 % of total; 46 % of PwID) and 20 moderate-profound 20 (14.4 % of total; 54 % of PwID). 102 had no ID. A further 177 patients were identified and approached but did not consent to this study. Severity of ID was not collected for potential participants, but ID and no ID refusal rates were similar to participation rates, with 23.2 % of non–participants PwID (n41 of 177). The sample size of $n = 102$ people without ID and $n = 37$ people with ID provides 81 % power at a significance level of 5 % to detect a group difference in drop-out rates of 26 %, assuming a rate of 50 % in the non-ID group.

3.2. Participant baseline characteristics

Baseline characteristics for the overall group of research participants and by ID type (with p-values for testing for association with severity of ID) are detailed in Table 2, along with BRV starting and maximum dose. P-values relate to a test of association between baseline characteristic and ID severity (categorised as no ID/mild ID/moderate-profound ID).

PwID recruited to the study were more likely to be younger ($P < 0.001$), male ($P < 0.005$) and to have existing neurodevelopment conditions ($P < 0.001$). Other comorbidities (mental health and physical health) were comparable across groups. Mean starting dose of BRV was slightly higher for the no ID group (57 mg compared to 49 mg for PwID) but this difference was not statistically significant. Mean maximum dose was also slightly higher for the no ID group (152 mg) and increasingly lower with severity of ID (150 mg for mild ID and 137 mg for moderate-profound ID) but these differences were also not statistically significant.

Table 2
Baseline characteristics and medication dose of overall cohort.

Characteristic	All patients N (%)	No ID	Mild ID	Moderate-profound ID	p-value
Age					<0.001
<30	38 (27.9)	15	9	14	
30–40	30 (22.1)	25	2	3	
40–50	30 (22.1)	25	3	2	
>50	38 (27.9)	34	3	1	
Missing	3	3	0	0	
Gender					0.005
Male	55 (39.6)	32	11	12	
Female	84 (60.4)	70	6	8	
Physical health condition					0.165
Yes	80 (57.6)	54	11	15	
No	59 (42.4)	48	6	5	
Mental health condition (non-psychotic)					0.336
Yes	53 (38.1)	40	8	5	
No	86 (61.9)	62	9	15	
Mental health condition (psychotic)					0.208
Yes	12 (8.6)	7	3	2	
No	127 (91.4)	95	14	18	
Neurodevelopmental condition					<0.001
Yes	33 (23.7)	5	11	17	
No	106 (76.3)	97	6	3	
Dose					
Mean starting dose	55	57	49	49	0.685
Mean max dose	150	152	150	137	0.745

3.3. Response to BRV

Tables 3-6 and Figs. 1-4 provide the details of the response to BRV. Overall across all groups, efficacy of BRV (>50 % seizure reduction at 12 months) was 30.2 %. The observed efficacy proportions were higher in both ID groups than in the no ID group, but these differences were not statistically significant in univariable analysis ($p = 0.913$; Table 3). Similar findings were obtained in multivariable analysis, after adjustment for age, gender and baseline health conditions (Fig. 1). When the efficacy rate for all PwID (32.4 %) was compared with rate for the no ID group (29.4 %) this difference was also not significant ($p = 0.260$). Across the whole cohort of research participants, those aged 40–50 and 50 + reported significantly better efficacy outcomes than those aged <

Table 3
Change in seizure frequency (efficacy) by ID group.

	All patients (n = 139)	No ID (n = 102)	Mild ID (n = 17)	Moderate/ Profound ID (n = 20)
At least 50 % improvement	42 (30.2 %)	30 (29.4 %)	6 (35.3 %)	6 (30.0 %)
No improvement/less than 50 % improvement	97 (69.8 %)	72 (70.6 %)	11 (64.7 %)	14 (70.0 %)

Table 4
Risk of withdrawal by ID group.

	All patients (n = 139)	No ID (n = 102)	Mild ID (n = 17)	Moderate/Profound ID (n = 20)
Yes	35 (25.5 %)	27 (27.0 %)	4 (23.5 %)	4 (20.0 %)
No	102 (74.5 %)	73 (73.0 %)	13 (76.5 %)	16 (80.0 %)
Missing	2	2	0	0

Table 5
Risk of physical side-effects by ID group.

	All patients (n = 139)	No ID (n = 102)	Mild ID (n = 17)	Moderate/Profound ID (n = 20)
Yes	23 (16.5 %)	17 (16.7.0 %)	2 (11.8 %)	4 (20.0 %)
No	116 (83.4 %)	85 (83.3 %)	15 (76.5 %)	16 (80.0 %)

Table 6
Risk of mental health and behavioural side-effects by ID group.

	All patients (n = 139)	No ID (n = 102)	Mild ID (n = 17)	Moderate/Profound ID (n = 20)
Yes	28 (20.1 %)	18 (17.6 %)	6 (35.3 %)	4 (20.0 %)
No	111 (79.9 %)	84 (82.4 %)	11 (64.7 %)	16 (80.0 %)

30, (P = 0.02, P = 0.05 respectively) after accounting for ID severity (Fig. 1).

Across all participants, the withdrawal rate for BRV at 12 months was 25.5 % (retention 74.5 %). Although the observed retention was slightly higher in both ID severity groups (76.5 % n13 – mild ID, 80.0 % n16 mod-profound) than in the no ID cohort, these differences were not statistically significant in univariable analysis (p = 0.660; Table 4) or multivariable analysis (Fig. 2). When retention at 12 months for all PwID (78.4 %) was compared to the no ID group (73.0 %), this difference was also not significant (p = 0.373).

Overall, physical and mental/behavioural side effects were reported within 12 months of BRV first prescription for 16.5 % and 20.1 % of participants respectively (Tables 5 & 6). Physical side effects were similar across age, gender and ID group, with no statistical associations with ID severity in univariable (p = 0.869; Table 5) or multivariable comparisons (Fig. 3). Despite an observed increase in mental and behavioural side-effects in the mild ID group, ID severity was not significantly associated with side effect risk in univariable (p = 0.255; Table 6) or multivariable analysis (Fig. 4). Mental and behavioural side-effects were more prevalent across the combined ID group when compared to those with no ID, (27.0 % for PwID, 17.6 % for no ID) but again effect this was not statistically significant (p = 0.441).

4. Discussion

We report on the first multi-site (n12) study detailing the efficacy and tolerability of BRV, where PwID with differing severity are compared with participants with no ID. There were no statistical differences in each of our four key outcomes (efficacy, tolerability, physical and mental health side effects) when comparing all PwID in our dataset with those with no ID or when assessing associations with severity of ID. UK NHS research participants in our study responded similarly to BRV irrespective therefore of whether they had an ID or its severity. These outcome data build on other observational real world research studies of BRV for PwID described in our introduction and detailed in Table 1. Findings across the literature broadly support the prescribing of BRV for PwID. Our study adds to these data by also detailing similar response for those with mild ID and moderate-profound ID.

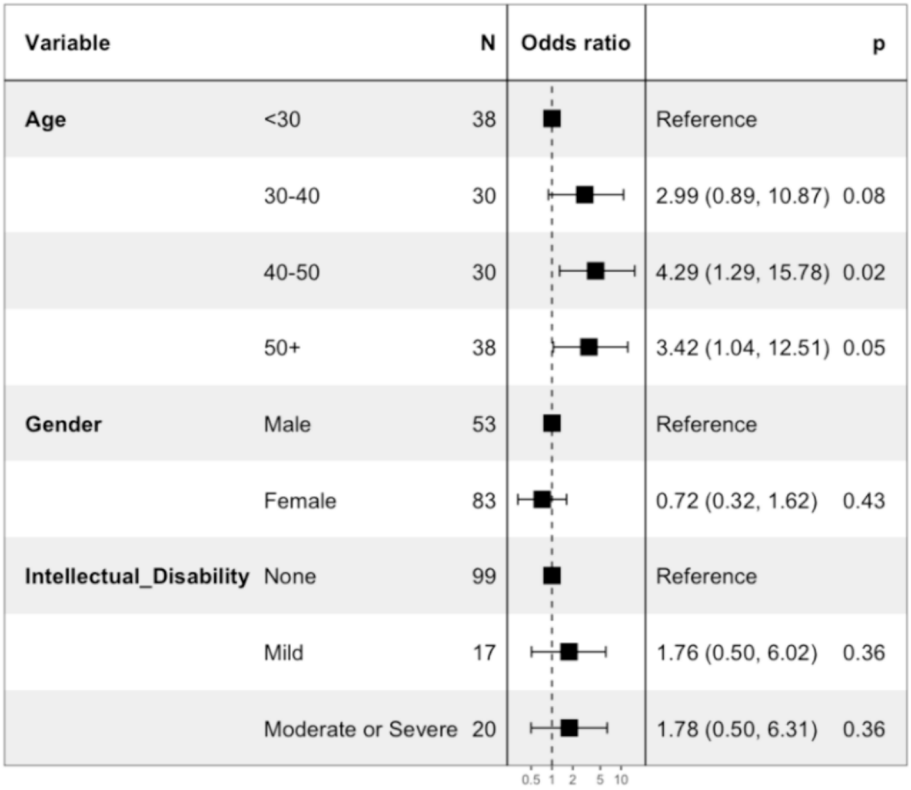

Fig. 1. Logistic regression analysis of efficacy (>50 % seizure reduction) in participants initiating BRIV.

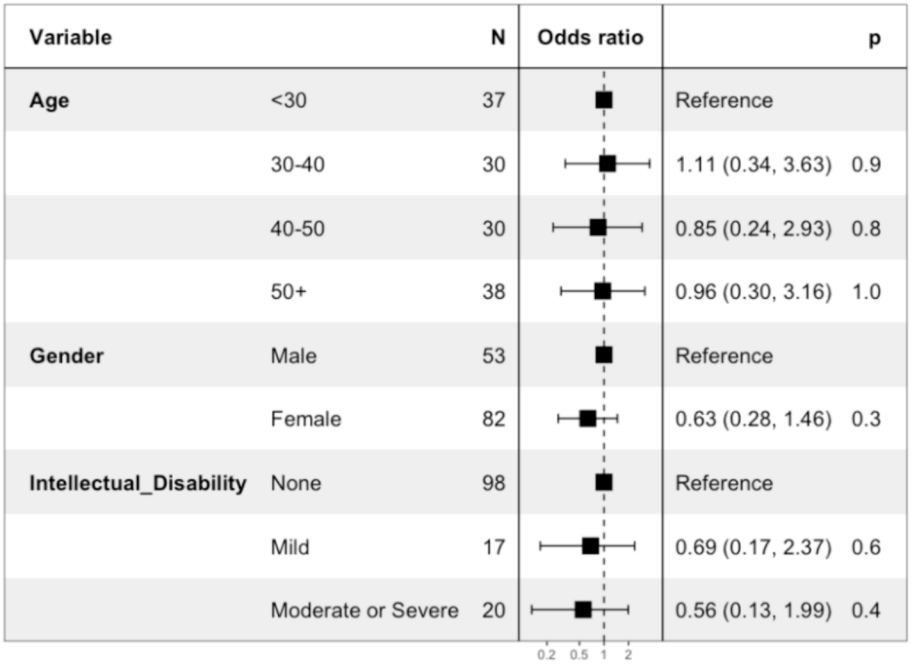

Fig. 2. Logistic regression analysis of risk of withdrawal in participants initiating BRIV.

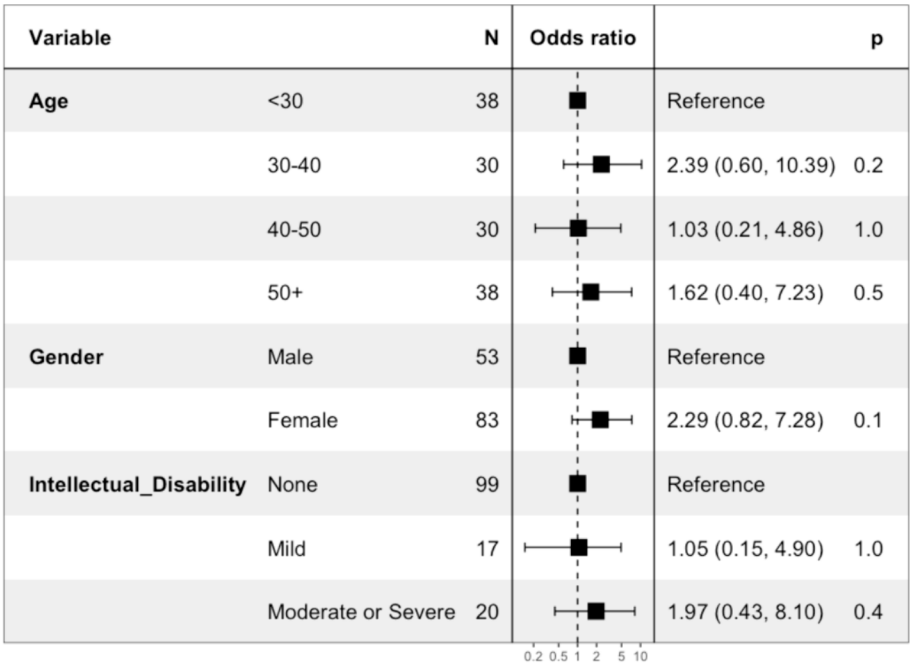

Fig. 3. Logistic regression analysis of risk of physical side-effects in participants initiating BRIV.

Our twelve-month retention rate for our full ID population (74.5 %) is higher than previously published studies (table 1). The no ID research participants in our dataset also report slightly higher twelve-month retention rates (73 %) compared to previous reported studies. Our findings are similar to other reported studies which compare PwID and those with no ID, where participants with ID have slightly higher, but non-significant retention rates [23,21,22]. Both studies who included those with different severity of ID had lower retention rate for all PwID (37.0 % and 58.1 %) than our study at twelve months, but this was reported only across the ID patient populations [18,24]. The larger study also reported a breakdown at six months for combined borderline/mild/moderate (78.3 %) and severe/profound (68.0 %) ID patients [24]. Retention was only slightly lower than our 12-month data for all PwID (78.4 %) and similarly not significantly associated with ID severity ($p = 0.307$).

Twelve-month efficacy data for PwID varies across previous studies (19 % −37 %), with three of four studies reporting '>50 % seizure improvement' as lower for PwID compared to no ID cohorts (Table 1). This includes the largest study (n182 PwID), which reported significantly lower response for PwID (32.2 %) compared to those with no ID (43.4 %) [22]. Our study found the opposite (32.4 % ID verses 29.4 % no ID) but with smaller numbers (n37) and no statistical significance. Only

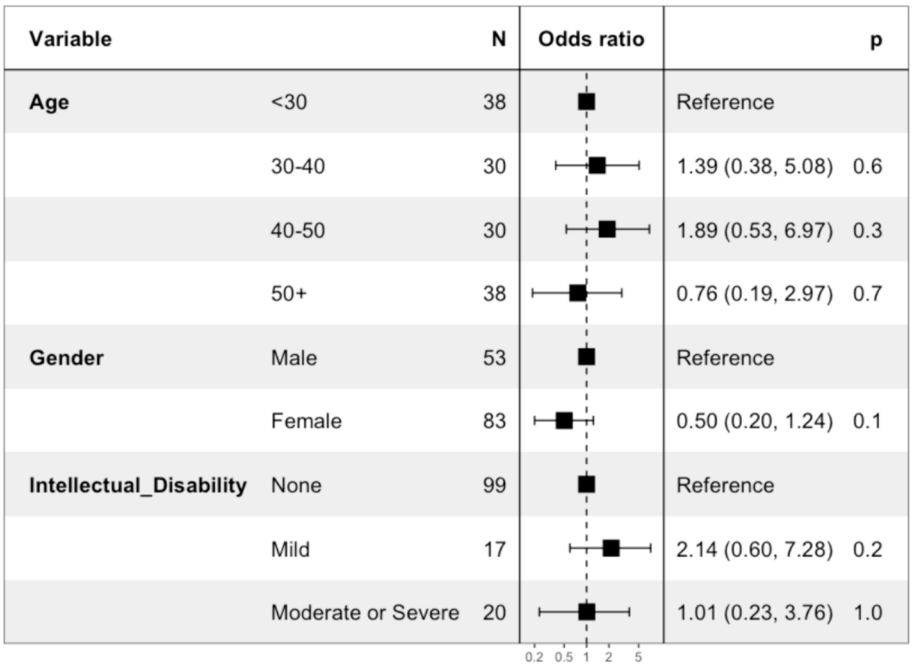

Fig. 4. Logistic regression analysis of risk of mental health and behavioural side-effects in participants initiating BRIV.

one study compared ID severity efficacy data for '>50 % seizure improvement', but in this instance at six months, with; 23 % (n3) for 'borderline/mild ID' and 30 % (n6) for moderate/severe ID patients [18]. Our data (35.5 % mild and 30.0 % moderate-profound) suggests better efficacy across our larger dataset at twelve months. Our efficacy data highlighting a statistically better response for research participants who are over 40, suggests that BRV is more effective in older NHS patients in our research population. This data account for ID severity, with the trend similar across groups. Post-hoc analysis of clinical trial data has suggested BRV may be a promising ASM for older adults, [31]. Analysis of the BRIVAFIRST study in Italy also supports the use of BRV in the older (>65 year of age) population [32]. Elsewhere one specific study found efficacy was better in the older population [33]. Our study findings on older adults appear consistent with these.

Mean start dose for PwID prescribed BRV also varies considerably across other observational studies detailed in Table 1 (25mgs – 200mgs). Our reported mean start dose (57 mg no ID, 49 mg mild ID, 49 mg moderate-profound ID) is closer for ID and no ID groups than reported elsewhere, whilst our data details similar mean maximum dose (152 mg, 150 mg, 137 mg), which reduces slightly with severity. These data indicate that UK Clinicians have taken the level of ID into consideration when prescribing for our research participants. This also reflects the guidance and trend in clinical practice for prescribing more cautiously for PwID [27,28,29,16], [11]. The other study reporting BRV dose across different ID groups only reports dose related to efficacy for research participants rather than ID severity [18]. Our study does not detail the relationship between efficacy and dose, but our comparable efficacy data across groups is evident whilst PwID are prescribed a slightly lower mean start and maximum dose.

There is a higher rate of mental health and behavioural side effects reported for PwID in our dataset, but unlike some previous studies these differences were not significant. As detailed in our introduction, the complex clinical picture for PwID and epilepsy means that this population can be more vulnerable to such side effects. Findings have however varied with different medications studied with our Ep-ID register [27,28,29] and there are challenges regarding such data for PwID, including the potential underreporting of adverse events [34]. As with other arms we report on side effects for those with differing severity of ID, with our data indicating a higher prevalence of mental health and behavioural side effects for those with Mild ID, but with small numbers and no significance. The single other study reporting side-effects for different ID populations also found that level of ID did not impact on side-effects reported [24].

A third of our sample, (47/139) were being prescribed LEV before switching to BRV. Strikingly, this was approximately a third of patients of each sub-group i.e. 35 of 102 'no ID', 6 of 20'mild ID', and 6 of 17'Moderare-Severe ID'. A recent study [35] compared LEV between those with ID and non-ID. This study had 173 PwID and 200 without ID. Significant association emerged between ID severity and psychiatric adverse effects ($P = 0.035$). Another study [36] focused on LEV to BRV switch in 77 participants of whom 46 had ID. Prior switch, psychiatric adverse effects were reported from LEV in 59 % in PwID and 68 % in those without ID. Seizure reduction of > 50 % was seen in 40 % patients along with a 90 % retention rate after 12 months in the cohort. The high proportion of patients in this study being prescribed LEV prior BRV suggests clinicians see BRV as an alternative to LEV to provide improved psychological outcomes accentuated with an ease of transfer between the two ASMs. However, we can't say with any definitiveness if the prescribing of BRV was influenced by LEV's effectiveness or side effects in the participants as this is not detailed in the dataset.

4.1. Limitations

More than half of NHS patients approached to participate in this study did not participate. Our data should be considered in the context of a specific population of NHS patients who were happy to engage with the research process and to provide consent to data being collected form their medical records. It is not therefore representative of all patients prescribed BRV at our study sites. Case-note based retrospective study the ethics of the study requires either informed consent or assent (if concapacitous participant) from a family member to access the patient record. Number of PwID and no ID research participants are therefore smaller than some other multi-site studies. Recruitment was completed between 2020–2022 which meant that many PwID (or carers) were approached through postal invite rather than face-to-face in clinics which has occurred in other Ep-ID arms. This was due to many NHS Trust providing remote online clinics due to the COVID 19 pandemic. This impacted on opportunity for researchers at DCCs to discuss the

study in person with patients and carers and may have also impacted on recruitment rates. Further limitations were those found with similar case-note retrospective studies such as poor seizure description and associated data of interest, possible bias in recruitment and badly described side effects and possibly inadequate sub-group samples of PwID. Furthermore, given the low numbers and risk of underpower caution is needed in interpreting the efficacy results.

5. Conclusion

The data reported from our study of BRV and the discussion of our findings in the context of the other real-world observational data reported since BRV was licenced, indicate that BRV may be an appropriate ASM for PwID. Findings indicate that BRV is largely well tolerated and can be effective for a proportion of PwID and that response is similar for those with different levels of ID severity.

CRediT authorship contribution statement

Jon Allard: Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **William Henley:** Writing – review & editing, Visualization, Validation, Software, Funding acquisition, Formal analysis, Data curation. **Adrian Sellers:** Writing – review & editing, Resources, Investigation, Data curation. **Emma O'Shaughnessy:** Writing – review & editing, Project administration, Investigation, Data curation. **Oliver Thomson:** Writing – original draft, Visualization, Investigation, Formal analysis. **Brendan McLean:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Mary Parrett:** Writing – review & editing, Project administration, Data curation. **Sanjeev Rajakulendran:** Writing – review & editing, Visualization, Validation, Project administration, Investigation, Data curation. **Lance Watkins:** Writing – original draft, Validation, Project administration, Methodology, Data curation. **Melissa Maguire:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Shan Ellawela:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation. **Phil Tittensor:** Writing – review & editing, Investigation, Data curation. **Arjune Sen:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Data curation. **Rajiv Mohanraj:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Manny Bagary:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Data curation. **Sunil Ram:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Allan Brown:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Rohit Shankar:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: UCB pharma provided an investigator initiated support grant which part paid the research co-ordinator JA's time. PT has received honoraria and support for educational projects from UCB Pharma. AS hold a current research grant with UCB Pharma looking at the possible immune basis for drug resistance in epilepsy. It is not a direct conflict with the manuscript. AS and the Oxford Research Group have received institutional and research support from Bial, Eisai, Livanova, UCB Pharma. RS has received Honoria, institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Angelini, UnEEG and Jazz/GW pharma outside the submitted work. He holds grants from NIHR AI, SBRI and other funding bodies all outside this work. No other author has any declared conflict of interest related to this paper.

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Statements and Declarations including competing interests

The authors acknowledge that UCB has funded this work and other research activities of the authors. This Research Database is however approved by NHS ethics and adopted on the National Institute for Health Research portfolio. UCB has no input into the design or study implementation. Individuals collecting the data are research staff or clinicians not funded by UCB who support research activity within their NHS Trust. The study is also open to independent site inspection.

Ethics statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Author contributions

All authors satisfy the ICMJE guidance by substantially contributing to the design, analysis and interpretation of the work, drafting of the manuscript, final approval of the manuscript and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work is appropriately investigated and resolved.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Rationale of combining the moderate – Profound ID [37]

1. Each of the 3 sub-groups of moderate, severe and profound ID have a low prevalence among the ID population (10 % moderate ID, 4 % severe ID, and about 2 % profound) and together they would combine to form 15 % of the total ID population. Taken individually it would be difficult to achieve satisfactory power to deliver meaningful conclusions.
2. The 3 groups are difficult to assess and diagnostically classify with any significant confidence which causes significant issues with accuracy of specific diagnosis of Moderate, severe or profound ID.
3. The 3 groups of moderate, severe and profound ID are defined by qualitatively significantly higher levels impairments. Where people with mild ID have near independent lives with some or minimal support, those with moderate to profound ID tend to be supported and supervised at all times.
4. Impairments such as communication difficulties, making informed choices and needing supervision is similar in the 3 groups of people with moderate, severe and profound ID, People with mild ID can make informed choices on most day-to-day matters and can be supported to provide a personal view on medication choice, compliance and reporting side effects.

5. Epilepsy possibly due to disturbed brain function is present in 30–50 % of the Moderate to Profound ID group as compared to 8–12 % in the mild ID population and 0.6–1% in general population.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109906.

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