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Efficacy and tolerability of levetiracetam in people with and without intellectual disabilities: A naturalistic case control study

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ABSTRACT

Introduction: People with Intellectual Disabilities (PwID) are twenty times more likely than general population to have epilepsy. Guidance for prescribing antiseizure medication (ASM) to PwID is driven by trials excluding them. Levetiracetam (LEV) is a first-line ASM in the UK. Concerns exist regarding LEV's behavioural and psychological adverse effects, particularly in PwID. There is no high-quality evidence comparing effectiveness and adverse effects in PwID to those without, prescribed LEV.

Methods: Pooled casenote data for patients prescribed LEV (2000–2020) at 18 UK NHS Trusts were analysed. Demographics, starting and maximum dose, adverse 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: 173 PwID (mild 53 M/P 120) were compared to 200 without ID. Mean start and maximum dose were similar across all groups. PwID (Mild & M/P) were less likely to withdraw from treatment ($P = 0.036$). No difference was found between ID and non-ID or between ID groups (Mild vs M/P) in LEV's efficacy i.e. >50 % seizure reduction. Significant association emerged between ID severity and psychiatric adverse effects ($P = 0.035$). More irritability (14.2 %) and aggression (10.8 %) were reported in M/P PwID.

Conclusion: PwID and epilepsy have high rates of premature mortality, comorbidities, treatment resistance and polypharmacy but remain poorly researched for ASM use. This is the largest studied cohort of PwID trialled on LEV compared to general population controls. Findings support prescribing of LEV for PwID as a first-line ASM.

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1. Introduction

1.1. Multifaced challenges of intellectual disability (ID) and epilepsy

Data from international studies suggest epilepsy prevalence in people with Intellectual Disability (PwID) is around 22.2 % [1] and significantly higher than estimations of 0.8 % for the general worldwide population [2]. UK data shows similar distributions, with 17.9 % of PwID having an NHS epilepsy diagnosis, compared to 0.6 % of those with no ID [3]. Prevalence increases with severity, with 7.3 %−9.8 % of people with mild ID and 27 %−41.6 % with moderate to profound ID diagnosed with epilepsy [1].

Intellectual Disability (ID) is the incomplete development of cognition, characterized by impairment of skills during the developmental period, which contribute to the overall level of intelligence, i.e. language, cognitive and social abilities and an IQ of less than 70 [4]. Clinical trials of antiseizure medications (ASM) have continued to exclude this complex and vulnerable population [5], with prescribing guidelines for ASM often recommending non-specific additional monitoring of effectiveness and tolerability whilst replicating treatment guidance for the general population [6,7]. Specific prescribing recommendation can therefore remain tentative and unclear for this group of PwID and epilepsy [8].

There are additional concerns for PwID and epilepsy which go beyond just the epilepsy. Uncontrolled epilepsy impacts significantly on the quality of life of PwID [9], with associated impacts on families and paid carers [10]. Higher rates of physical and mental health co-morbidity are evident [11], along with significant associated increased risk of mortality, particularly when seizures are ongoing [1, 12,13]. Four in ten of all potentially avoidable emergency admissions for PwID in England result from 'convulsions and epilepsy' [14], whilst Sudden Unexpected Death in Epilepsy (SUDEP) is identified as the second most common cause of death in PwID and epilepsy, with a Standardised Mortality Ratio (SMR) of over 30 comparing PwID and epilepsy to general population [13,15].

Identifying appropriate epilepsy treatments for PwID is therefore important but can also be complex. Treatment resistance, polypharmacy, side effects and cost to treat have all been found to higher for those with ID [16–20]. Communication difficulties and potential misinterpretation of symptoms and behavioural or psychological events [21], coupled with the risk of missing adverse effects [5] add to this complex clinical picture. The Cochrane systemic review of randomised controlled trials (RCTs) of ASM in PwID, broadly support their use to reduce seizure frequency, but also identifies a paucity of high-quality studies and limited behavioural and cognitive safety data [22].

ID is characterised by deficits in intellectual functioning and adaptive behaviour, covering many every day and practical skills, including those related to cognition and communication [23]. These develop before the age of 18, persist lifelong and vary with severity across the estimated 10.37/1000 of the international population who have ID [24] In addition to increased epilepsy prevalence those with more severe ID are also less likely to respond to epilepsy treatments [25] Generating data to inform prescribing practice may therefore benefit from studying different populations of PwID.

1.2. The EP-ID register

Here we report on one arm of a Research Database Register for UK NHS patients who have epilepsy and ID (referred to as the Ep-ID Register in this paper and detailed below). This multi-site NHS collaboration has focussed on the need to build the evidence base for use of new ASM in PwID [26]. Between 2014 and 2020 the register focussed on post 2004 ASM [27–29], before widening to focus on all ASM along with epilepsy treatments following NHS ethics extension and amendment. The Ep-ID register does not only compares response to ASM for PwID and people with epilepsy from the general population but also focuses on comparing response for those with mild ID to moderate and profound ID.

1.3. Levetiracetam and intellectual disability

Levetiracetam (LEV), a second generation ASM which was identified in the 2015 Cochrane review and recent research as in specific need for more focussed investigation of its efficacy for those with ID [22,30], It is the first study arm of the NIHR Ep-ID research register focussed on an ASM licenced in the UK before 2004. Till date, previous studies of the Register have focused on ASM licenced post 2008 primarily for pharmaco-resistant epilepsy. LEV is licensed in the UK for monotherapy of focal seizures with or without progression to bi-lateral tonic-clonic seizures, as adjunctive therapy of focal seizures with or without progression to bi-lateral tonic-clonic seizures, and as adjunctive therapy of myoclonic seizures and generalised tonic-clonic seizures [31]. It has a novel mode of action, the precise mechanism for which remains unknown, and is structurally and mechanistically unrelated to other ASM, except for brivaracetam. In animal models LEV has been shown to bond to synaptic vesicle protein SV2A [32]. SV2A may participate in the exocytosis of synaptic vesicles and regulate the release of neurotransmitters, supressing epileptic discharge [33].

LEVs clinical efficacy for seizures reduction, limited interaction with other drugs, and tolerability, mean it is one of the most widely prescribed ASM used in routine clinical practice [34]. It is the most commonly prescribed ASM in the UK, following its introduction in 2000 [33]. A recent Cochrane Review of ASM supports its use as monotherapy [35], whilst a 2019 systematic review of the literature examining the safety and efficacy of LEV, found it was comparable with other widely prescribed ASM [33].

While there has been no RCT of LEV for PwID, a number of open label studies have demonstrated that as a second-line treatment it is effective and generally well-tolerated by the ID population, with low risk of interaction with other commonly prescribed ASM [7]. A multi-centre prospective study of LEV as an add-on treatment based in Wales, found median seizure frequency reduced from 4.2 to 2.2 ($p < 0.05$) for the 30 research participants still in the trial at six months [36]. Another small UK study found 3 of 21 participants (14 %) were seizure free and 9 (43 %) showed >50 % reduction at twelve months [37]. Data around behaviour and adverse effects were minimal or limited in reporting in both studies. A Norwegian study ($n = 184$) compared efficacy and tolerability of LEV for patients with ID ($n = 56$) and without ID ($n = 128$) [38]. Participants were followed for varying periods with LEV (mean 8.1 months) and found to be similarly effective and tolerated across groups, with 39 % (37 % PwID and 40 % no ID) having $a > 50$ % seizure reduction reported. The study also reported that 32 % of patients with mild ID and 44 % with Severe ID had >50 % seizure reduction. Sedation was the most common reported adverse-effect, whilst behavioural adverse effects were more common for those with ID compared to those without ID (23 % compared to 10 %).

A recent retrospective observational study of LEV and children with ID ($n = 298$, 151 'ID', 147 'no ID') focussed on paediatric patients of school age in South Korea [30]. This study found encouraging results at 6 months, with 96 % of 'no ID', and 83 % 'ID' reporting >50 % seizure reduction ($p = 0.031$). Retention was approximately 75 % across both groups at 24 months with under 15 % of children reporting similar adverse-effects, to the studies detailed above including sedation. Elsewhere the most common adverse effects reported for those with ID prescribed LEV include fatigue, somnolence, dizziness, and upper respiratory tract infection, mostly mild to moderate in intensity and occurring during the initial titration phase [39,40].

Studies have also found an association between LEV and psychiatric and behavioural adverse effects (particularly aggression), for PwID. That may possibly be the primary factor for drug discontinuation beyond the initial titration period [41]. A post marketing survey of 354 UK patients (and carers) across all age groups including all populations found that while sedation was the most common adverse effect reported

(in 11 %), mood disturbance (5 %) and behavioural disturbances and/or psychosis (3 %) were more likely to lead to discontinuation [40]. UK NICE Guidelines (2012) also note that clinicians often consider changes in behaviour to be common adverse effects of LEV [42].

2. Methodology

This was a multi-center retrospective evaluation of treatment with data collected from 18 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 adopted (NIHR 31,484) 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 (LEV), were collected at 18 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 ASM [27–29].with research staff and clinicians at new sites receiving support and training for recruitment and data collection processes as required.

2.1. Eligibility and consent

All sites screened electronic record systems and databases to identify people aged 18 or over who were currently or previously prescribed LEV. Potential research participants were asked to consent to retrospective collection of confidential and anonymous pre-existing and routine clinical data recorded in their NHS medical records. NHS Patients were either recruited face-to-face during routine clinics, or by letter requesting return of consent forms or consultee declaration forms (assent) in stamped addressed envelopes. Where sites did not have capacity to contact all people currently or previously prescribed LEV, a proportion of individuals - representative of the Trust's patient population, were identified. This was determined by local resources at DCCs and involved either a random sampling of all eligible patients, focussing on a specific epilepsy Practitioners caseload, or focussing on those prescribed LEV from a period when accurate electronic medical records were available. The statistical team was involved in advising on the stratification principles employed. PwID were provided with 'Easy Read' information sheets and consent forms. Where patients lack capacity to consent, a patient consultee was approached regarding the individual's participation in the research project. Consultees were identified through clinical teams and asked to complete carer consent forms if they were willing to support patient participation.

2.2. Data collection and categorisation

The pre-existing, feasibility tested and standardised Ep-ID data collection tool was applied [27]. Data collected included demographics, current and historical clinical health data related to epilepsy, ID classification and severity. PwID were categorised as 'mild' or 'moderate-profound' following ICD-10 classifications. The rationale for combining moderate to profound ID is provided in appendix 1. Health comorbidities were categorised into physical, mental (psychotic and non-psychotic), neurodevelopmental, and others. Data related to LEV and concomitant ASM were collected for a fifteen-month period (three-month period prior to commencement of LEV and twelve months post commencement). Data were collected on dosage, withdrawal within twelve months and reason for withdrawal. Common adverse effects as listed in the UK British National Formulary (BNF) along with any uncommon adverse were collected. This involved researchers at study sites mining consultant and epilepsy nurses clinical letters for adverse effects recorded during clinical consultations and either confirming a BNF adverse effect in the data collection tool or adding verbatim information regarding other adverse effects.

Seizure frequency was collected as monthly seizure totals, identified from medical records at the five time points. Changes from baseline after twelve months, or earlier if LEV was withdrawn during the study period, were categorised as either 'Worsening', 'No change', or percentage improvements equivalent to or greater than '25 %', '50 %' or '75 %+'. This involved researchers directly comparing the documented number of seizures reported in clinical records at time point two (first prescription) and the documented number of seizures reported at time point four (12 months post first prescription) or using verbatim quantified improvement documented in medical records. If it was not possible to quantify scores into the pre-determined categories researcher were directed not to do so. Researchers were asked to focus on any seizure count documented and did not therefore focus on specific seizure type. Research participants were also categorised into those with "At least 50 % improvement" and "No improvement/less than 50 % improvement" following 12 months LEV treatment. This was done post data collection and by the study Statistician. 50 % and 75 % improvement were re-coded into "At least 50 % improvement" with all other scores re-coded into "No improvement/less than 50 % improvement".

Data were pseudonymised with each research participant given a numerical ID and transferred securely to the sponsor site via NHS Mail in a standardised, password-protected format. Identifiable data (patient ID numbers and consent forms) remained at the DCCs. Data collected were standardised to account for any inconsistences with data queries raised with DCCs where appropriate.

2.3. Analysis

Baseline data, including non-identifiable demographic and diagnosis specific health data, were summarised by the median and interquartile range (IQR) for continuous data, and the number and percentage for categorical data. Univariable ID group comparisons of quantitative baseline characteristics were conducted with the Mann-Whitney test. Fisher's exact test was used for assessing univariable associations between ID group and categorical baseline characteristics.

Follow-up data, including information relating to the intensity and frequency of seizures and the adverse effects associated with LEV, were summarised using a similar approach. Univariable analyses were conducted with Fisher's exact test to assess the association between ID group and the study outcomes: efficacy (at least 50 % improvement in seizure frequency), retention and risk of adverse effects at 12 months after initiating LEV treatment. In the primary analyses, outcomes for individuals from the general population were compared with those with ID. Different ID groups were compared in secondary analyses. Due to potential differences in baseline and demographic variables between groups, further analysis of the study outcomes was performed using logistic regression methods to assess ID group differences after adjustment for potential confounders (e.g., age, gender and baseline health conditions). Factors found to vary between groups in the univariable analysis were considered for inclusion as covariates in the regression analysis. A complete cases approach was used to handling missing data. A complete case approach utilises only the cases in a data set for which there are no missing values on any of the key variables of interest. All analyses were performed using the R environment for statistical computing.

2.4. Power

Power calculations were conducted to determine the effect sizes that could be detected with the available sample when comparing outcomes

between PwID and the general population. The sample size of $n = 200$ patients without ID and $n = 173$ patients with ID provides 84 % power at a two-sided significance level of 5 % to detect a group difference in efficacy of 15 % (Cohen's $h = 0.30$), assuming a rate of 50 % in the non-ID group (comparable to the 47.3 % responder rate of ≥50 % in the systematic review [33]. Similar effect size estimates were detectable when comparing PwID to the general population for withdrawals, and for physical and mental side-effects. Although the study was adequately powered to detect moderate-large effect sizes (Cohen's $h \geq 0.30$), it was underpowered to detect small effect sizes.

3. Results

Data were collected for 373 eligible research participants. An additional 57 people did not have a specific recorded date for when LEV was first prescribed (missing $n = 56$, invalid $n = 1$) and were excluded from the data reported in this paper. All 373 research participants were first prescribed LEV between February 2000 and November 2019, with the retrospective data collection period extending from February 2000 - November 2020 (allowing up to 12 months of post first prescription LEV data to be collected for all research participants).

Clinical features and demographic characteristics of research participants are detailed in Table 1. Testing for association with severity of ID (Mild and M/P) are also presented.

200 research participants had no ID, and 173 had ID. Of the PwID 53 had 'mild ID', whilst the other 120 had 'moderate-profound ID'. The association between Level of ID and age when first prescribed LEV was statistically significant ($P < 0.001$), with over four in five (83.2 %) of those with moderate-profound ID starting LEV under 40 years of age, compared to only half (51.0 %) of general population (no ID) research participants. Fig. 1 details a histogram showing the distribution of age at first seizure ($n = 339$, 34 missing). Fig. 2 details density plots showing distribution of age at first seizure split by ID group. Test of difference in median age at first seizure between all PwID and the non-ID group was significant ($P < 0.001$)

Table 1
Clinical Features of Patients who underwent LEV treatment.

	Overall (n = 373)	No ID (n = 200)	Mild ID (n = 53)	Moderate–Profound ID (n = 120)	p-value *
Age when starting LEV					<0.001
<40	237 (63.7 %)	102 (51.0 %)	36 (67.9 %)	99 (83.2 %)	
40–60	89 (23.9 %)	62 (31.0 %)	13 (24.5 %)	14 (11.8 %)	
60+	46 (12.4 %)	36 (18.0 %)	4 (7.5 %)	6 (5.0 %)	
Missing	1				
Gender					0.591
Male	190 (50.9 %)	97 (48.9 %)	28 (52.8 %)	65 (54.2 %)	
Female	183 (49.1 %)	103 (51.5 %)	25 (47.2 %)	55 (45.8 %)	
Existing conditions					
Physical health	245 (65.7 %)	129 (64.5 %)	32 (60.4 %)	84 (70.0 %)	0.408
Mental health (non-psychotic)	86 (23.1 %)	54 (27.0 %)	14 (26.4 %)	18 (15.0 %)	0.033
Mental health (psychotic)	20 (5.4 %)	7 (3.5 %)	4 (7.5 %)	9 (7.5 %)	0.210
Neurodevelopmental	113 (30.3 %)	21 (10.5 %)	26 (49.1 %)	82 (55.0 %)	<0.001

* p-value from Fisher's exact test for association between feature and severity of ID.

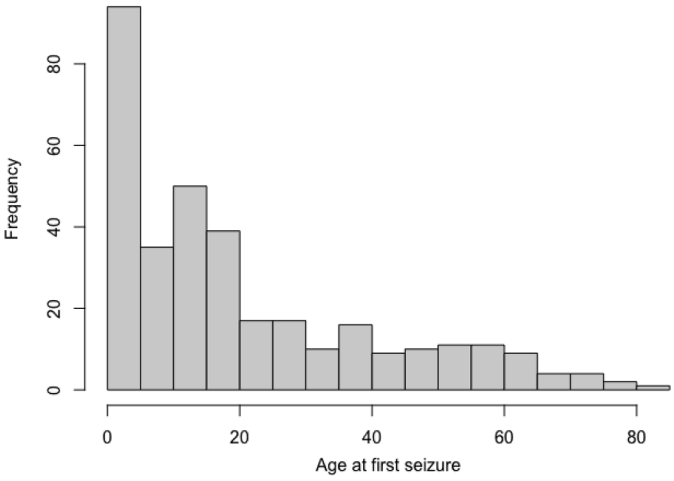

Fig. 1. Age at first seizure ($n = 339$, 34 missing).

Gender was similarly distributed across the study population (50.9 % male and 49.1 % female), with only slightly more male ID participants. An existing co-morbid physical condition was noted in 245 (65.7 %) of research participants with prevalence distributed similarly across PwID and those with no ID. Non-psychotic mental health conditions were reported in 23.1 % of all recruited people, but were less prevalent with increased ID severity ($p = 0.033$) and only reported in 15.0 % of those with moderate-profound ID. Psychotic mental health conditions were evident in one in 18 of all recruited participants (5.5 % across groups). Although psychotic conditions were more common in PwID (7.5 % for both ID groups, 3.5 % for those with 'no ID'), the association with presence of ID was not however statistically significant. Existing neurodevelopmental conditions increased significantly with severity of ID ($p < 0.001$) and were evident in over half (55.0 %) of those with 'mild ID' or 'moderate-profound ID' but just over one in ten (10.5 %) of 'no ID' research participants. Median age of first seizure for general population was 22 years (IQR 12–44) while it was 5 years for PwID (IQR 1–14) and was significant between general and ID groups ($p < 0.001$)

Table 2 provides the LEV mean and starting dose comparisions. Mean starting dose of LEV varied with research participants with no ID starting at a slightly higher mean dose (563.2 mg) than those with moderate-profound ID (547.8 mg) and 66 mg higher than those with mild ID (497.1 mg) ($p = 0.729$ for test of association between mean start dose and level of ID). Mean maximum dose was higher for those with mild ID (1446 mg) than research participants with no ID (1425 mgs) or those in the moderate-profound ID group (1333 mg) ($p = 0.631$ for test of association between mean maximum dose and level of ID).

Response to LEV treatment is presented in Tables 3–5. The observed efficacy level (>50 % improvement in seizure frequency) was higher in PwID than those with no ID (Table 3), with >50 % improvement for 54.7 % of 'no ID' research participants, 63.6 % for 'mild ID' research participants and 60.4 % for moderate to profound ID However, in univariable analyses, there was no association between efficacy and level of ID ($P = 0.464$), or between efficacy and binary ID groups ('Mild ID' vs. 'Moderate-Profound ID' and "all PwID" vs. "No ID") ($P = 0.253$). Similar findings were obtained in multivariable analysis, after adjustment for age, gender and baseline health conditions (OR for efficacy in binary ID group compared to No ID=1.27; 95 % CI=0.79–2.05; $p = 0.316$).

As detailed in Table 4, PwID were less likely to withdraw from LEV within twelve months (9.4 % 'mild ID' and 10.2 % 'moderate-profound ID' compared to 17.7 % for 'no ID'). There was no significant association

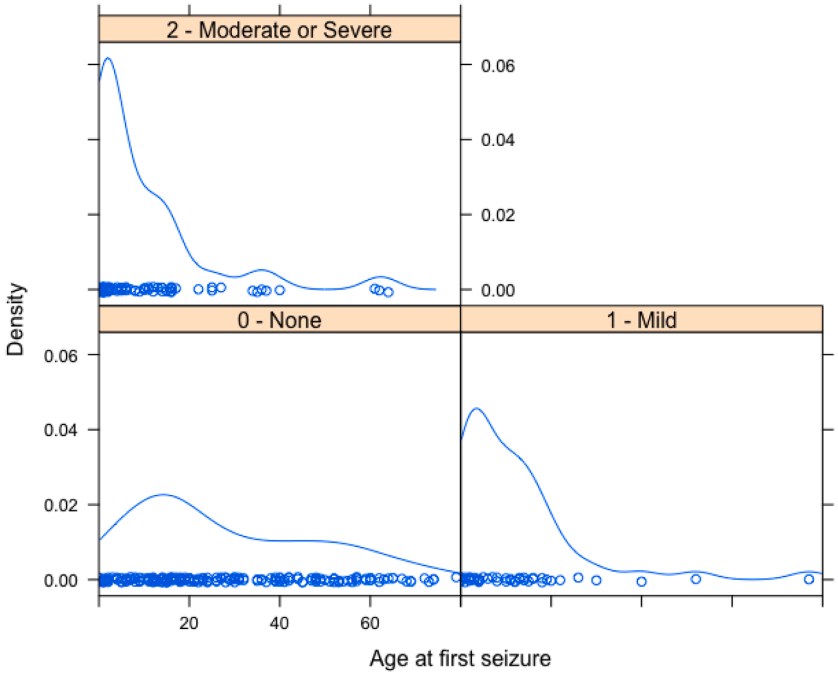

Fig. 2. Distribution of Age at first seizure (split by ID group).

Table 2
LEV dose and titration.

	No ID ($n = 200$)	Mild ID ($n = 53$)	Moderate/Profound ID ($n = 120$)
Mean start dose	563.2	497.1	547.8
Mean max dose	1426.0	1446.0	1333.0

Table 3
Seizure frequency (Efficacy).

	No ID ($n = 200$)	Mild ID ($n = 53$)	Moderate/Profound ID ($n = 120$)
At least 50 % improvement	93 (54.7 %)	28 (63.6 %)	61 (60.4 %)
No improvement/less than 50 % improvement	77 (45.3 %)	16 (36.4 %)	40 (39.6 %)
Missing	30	9	19

Table 4
Withdrawal (Tolerability).

	No ID ($n = 200$)	Mild ID ($n = 53$)	Moderate/Profound ID ($n = 120$)
Withdrawn			
Yes	35 (17.7 %)	5 (9.4 %)	12 (10.2 %)
No	163 (82.3 %)	48 (90.6 %)	106 (89.8 %)
Missing	2	0	2

between level of ID and withdrawal ($P = 0.115$) but when all PwID were compared to research participants with no ID, the difference in withdrawal was significant ($p = 0.036$). The association between withdrawal and the binary ID grouping failed to reach significance in multivariable analysis, with adjustment for age, gender and baseline health conditions (OR for risk of withdrawal in PwID compared to No ID=0.56; 95 % CI=0.29–1.06; $p = 0.080$).

There was no association between reason for withdrawal (identified as either 'increased seizures', 'intolerable', 'lack of efficacy' or 'other') and level of ID for the three groups ($p = 0.318$) and similarly where PwID were compared to those with no ID ($p = 0.223$). Physical and mental adverse effects are detailed in Table 5, whilst all adverse effects identified across ID groups and research participants are detailed in Table 6.

Table 5
Physical and mental adverse-effects.

	No ID ($n = 200$)	Mild ID ($n = 53$)	Moderate/Profound ID ($n = 120$)
Physical adverse effects			
Yes	35 (17.5 %)	10 (18.9 %)	29 (24.2 %)
No	165 (82.5 %)	43 (81.1 %)	91 (75.8 %)
Mental adverse effects			
Yes	27 (13.5 %)	5 (9.4 %)	27 (22.5 %)
No	173 (86.5 %)	48 (90.6 %)	93 (77.5 %)

Physical adverse effects reported in the first twelve months of LEV treatment were slightly higher for PwID, and increased with level of ID, but these differences were not significant (Physical adverse effects: p-value for association with 3 ID groups=0.335; p-value for comparison of all PwID with no ID=0.241)

There was a significant association between level of ID and mental adverse effects ($P = 0.035$), with adverse effects reported for 22.5 % of those with moderate-profound ID, and 13.5 % of those with no ID. Mental adverse effects were not however significantly higher for all PwID when compared to the no ID group ($p = 0.183$).

Drowsiness was reported in 11.3 % of the mild ID group and 8.3 % of the moderate-profound ID group, but less evident in the no ID group (5.5 %). Aggression was evident in 10.8 % of those with moderate-profound ID but far less prevalent for both the mild ID and no ID groups (3.8 % and 1.5 %), whilst irritability was evident in 14.2 % of the moderate-profound group and 9.0 % of the no ID group, but also less prevalent

Table 6
Individual adverse effects by ID group (key psychological adverse effects are in *italics*).

Adverse effect	No ID N(%)	Mild ID N(%)	Moderate/profound ID N(%)
Abdominal pain	0 (0.0)	0 (0.0)	2 (1.7)
Aggression	3 (1.5)	2 (3.8)	13 (10.8)
Anorexia	1 (0.5)	1 (1.9)	5 (4.2)
Anxiety	2 (1.0)	0 (0.0)	4 (3.3)
Ataxia	2 (1.0)	1 (1.9)	7 (5.8)
Convulsion	1 (0.5)	0 (0.0)	3 (2.5)
Cough	0 (0.0)	0 (0.0)	1 (0.8)
Depression	7 (3.5)	1 (1.9)	4 (3.3)
Diarrhoea	8 (4.0)	1 (1.9)	3 (2.5)
Dizziness	4 (2.0)	3 (5.7)	2 (1.7)
Drowsiness	11 (5.5)	6 (11.3)	10 (8.3)
Dyspepsia	2 (1.0)	0 (0.0)	1 (0.8)
Headache	6 (3.0)	1 (1.9)	0 (0.0)
Insomnia	3 (1.5)	0 (0.0)	7 (5.8)
Irritability	18 (9.0)	3 (5.7)	17 (14.2)
Malaise	3 (1.5)	1 (1.9)	5 (4.2)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	5 (2.5)	0 (0.0)	1 (0.8)
Rash	2 (1.0)	1 (1.9)	4 (3.3)
Tremor	2 (1.0)	2 (3.8)	1 (0.8)
Vertigo	1 (0.5)	0 (0.0)	0 (0.0)
Vomiting	2 (1.0)	0 (0.0)	3 (2.5)

in the mild ID group (5.7 %).

4. Discussion

Using the standardised Ep-ID Research Database Register methodology we present a real-world comparative observational study of PwID and epilepsy in England prescribed LEV as part of standard clinical care versus those from general population with epilepsy but without ID. Both study groups have been recruited from the same population. Similarities and differences between PwID and epilepsy (including those with 'mild ID' and those with 'moderate-profound ID') and people with epilepsy and 'no ID' prescribed LEV between 2000 and 2020, are presented.

Our dataset builds on the limited evidence base published around the use of LEV for PwID, whilst also providing specific data around those with both 'mild ID' and 'moderate-profound ID'. This study has a higher number ($n = 173$) of PwID prescribed LEV compared to previous open label studies reported with this patient population. The significant association between prevalence of neurodevelopmental conditions ($p < 0.001$) and age when first prescribed LEV ($p < 0.001$) with severity of ID, are consistent with clinical features and early onset and treatment of seizures for PwID [7,25]. Mental health (psychotic) and physical health conditions are slightly higher for those with ID in our dataset, but non-psychotic mental health conditions are more prevalent for those with no ID ($p = 0.033$).

Data from our research participants indicate that PwID in our study have a similar rate of >50 %+ improvement in seizures to those from the general population with epilepsy ($p = 0.253$ for efficacy). Univariable analysis showed that PwID in our study are less likely to have been withdrawn from LEV within twelve months of their first prescription, but this effect was no longer significant after adjustment for baseline characteristics. As detailed in our introduction, recent systematic and Cochrane reviews support the extensive scientific trial data generated from studies across people with epilepsy [33,35] Our study provides efficacy and tolerability data for PwID, which shows similar response to people with epilepsy who do not have ID. As indicated above, severity of ID was not associated with efficacy and tolerability in our dataset. This is comparable to the previous work in smaller patient groups [38].

Our twelve-month efficacy data for >50 %+ seizure reduction of 61 % of PwID for whom we have these data ($n = 145$) is higher than 43 % for much smaller patient numbers ($n = 9$) reported historically for the same period in the UK [37] and 37 % ($n = 20$) of patients with variable treatment length data (mean 8.1 months) reported in Norway [38]. A more recent study however has also found >50 % seizure reduction in 83 % of a similar number ($n = 151$), but in this instance it was school aged children with ID prescribed LEV for six months in Korea and not adults as in our study [30]. Comparison of retention rates to previous historical studies is restricted due to small numbers, varied timings and data inclusion criteria, but are also not dissimilar to the recent Korean paediatric population study where n120 (81 %) of the no ID population and 118 (78 %) of the ID population remained on LEV at twelve months [30], compared to n163 (82 % of no ID) and n154 (89 % for ID) in our study.

Our dataset also indicates similar prescribing practice for those with and without ID in mean start dose and mean maximum dose for LEV. There is minor variation between mean starting dose for those with 'mild ID' than those with 'moderate-profound' or with 'no ID' (497.1 mg compared to 547.8 mg and 563.2 mg). Further, there was no statistical difference in maximum dose achieved between groups. This is unexpected, as we know in general the approach to prescribing for people with ID, particularly moderate-profound is to start at lower doses with slow titration to minimise the risk of adverse effects, including lethargy and behavioural changes [7,8]. Our overall adverse effect data are similar to other studies and compares to the Korean (paediatric patients) and Norwegian studies with no significant differences between PwID and those with no ID. Our study does though highlight a significant association between severity of ID and reported mental adverse effects ($P = 0.035$) that is less evident in the other studies. The Norwegian did find similarly defined 'central nervous system' adverse effects were higher for those with 'no ID' but numbers across all groups were small (9 % 'no ID' $n = 11$, 4 % PwID $n = 2$) [38]. Previous studies have also highlighted the potential role of behaviour, mood and aggression for discontinuation of LEV [40]. Our data also provide insight into the variation across ID populations with both irritability and aggression reported as more prominent in the moderate-profound ID group. There is of course the possibility of reporting artefact from those who are more able to report adverse effects.

4.1. Limitations

There are various limitations with this study. Firstly, it is an open, retrospective research database study which is uncontrolled and reliant on secondary data collected by Researchers at different sites. As highlighted, it was not possible for example to identify a specific or appropriate start date for LEV from 57 research participants electronic medical records. Though not explicitly recorded, anecdotal evidence from sites, suggest this was primarily due to difficulty in identifying specific timelines for first prescription of LEV in electronically archived hard copies of historical medical records.

There is some missing efficacy data in our dataset (59 of the 373 research participants). Researchers reported difficulties in identifying specific quantifiable seizure frequency data from medical records for some research participants. Where this occurred, data were coded as missing. Further, as the seizures nomenclature varied considerably and as it is recognised PwID can have varied and mixed seizure types focus was only on the use of LEV irrespective of identified seizure type. Improvements in electronic record systems may mean these challenges regarding data identification and accuracy may reduce.

As detailed in our introduction there is a risk that adverse effects are missed and not documented for PwID who are prescribed ASMs. This includes the potential for patients who do not have ID being more capable of reporting adverse effects. This reporting bias should be considered alongside our adverse effects data, as well as other studies to which our data is compared. We also acknowledge the potential role of 'release phenomenon' [43], where improved seizure control following treatment has an impact on behavioural adverse effects rather than a specific ASM, to have impacted on our data.

The number of people prescribed LEV at certain DCCs, and

limitations of NIHR resources, meant that not all potentially eligible research participants were offered opportunity to enrol in this study. We did not collected data related to the number of people approached who did not consent (either refusal or implied refusal) to participate. Data reported are therefore representative of a sample of NHS patients (or carers) who were happy to consent to the collection of these data from their medical records, rather than all individuals prescribed LEV at participating NHS Trusts.

5. Conclusion

5.1. Implications for clinical practice

LEV is the most commonly used first line ASM in the UK today. Till date there was limited research on LEV's utility in PwID who form a significant minority of those with epilepsy. Our study evidence suggests that in our dataset LEV is as effective in PwID as in general population for management of seizures. It also suggests there is no major difference in side effect profile. Caution might need to be taken when prescribing in those with moderate to profound ID where there is an increased risk of irritability and/or aggression emerging. This is a single study with a small dataset with numerous limitations thus the interpretations need to be made cautiously.

5.2. Implication for policy

This study provides level 2 evidence on the utility of LEV for PwID. In the absence of a RCT for this population and the designed controls and sample size this study shows evidence for use of LEV in PwID.

5.3. Implication for research

The strength of post-trial observational data such as that presented in this paper have been highlighted [44]. This study demonstrates how database research methodology across multiple sites, such as those in the UK NHS, can help build such evidence. This offers potential to collect and analyse data around longer-term impact of ASM than reported in trial data, but also demonstrated potential to focus analysis on specific patient populations.

Statements and declarations including competing interests

RS has received 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.

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.

Declaration of competing interest

RS has received 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 to this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2024.05.010.

Appendix 1: Rationale of combining the moderate – profound ID

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 .

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