


Research Paper



Levetiracetam in epilepsy and autism spectrum disorder: analysis of safety, tolerability, and efficacy

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ABSTRACT

Purpose: One in five people with autism spectrum disorder have epilepsy and take Anti-Seizure Medications (ASM). However, the impact of ASM on people with autism is under researched. This study evaluates the efficacy and tolerability of Levetiracetam (LEV) for autistic people and epilepsy.

Method: Data was derived from the English Epilepsy Research Database Register which compares ASM responses in those with neurodevelopmental disorders to those without. Age range was 18–50 years as there were no autistic research participants with autism prescribed LEV over 50. Twelve-month ASM data, including withdrawal rate, seizure frequency and adverse effects were compared. Fisher's exact test was used to assess univariate associations between outcomes and autism with significance accepted as $p < 0.05$. Logistic regression was used to assess autism group differences after adjustment for potential confounders (age, gender, presence of baseline physical and mental health conditions).

Results: Of 175 (aged 18–50) research participants across 18 NHS Trusts, prescribed LEV between 2000 and 2020, 40 were autistic. There was no significant association between withdrawal rate ($P = 0.626$), or grouped side effects (physical $P = 0.165$, mental health $P = 0.791$). Autism was significantly associated with aggression with LEV in univariable analysis but this association was no longer significant after accounting for multiple testing. A significant non-linear relationship between efficacy and the autism group ($P < 0.001$) was found.

Conclusions: This study supports the use of LEV for people with autism and epilepsy as there is no difference in response noted to those without autism. However, they may have less prominent changes in efficacy.

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1. Introduction

Epilepsy, a disorder in the brain involving recurrent unprovoked seizures, is associated with greater risk of other health comorbidities [1]. This includes Autism Spectrum Disorder, a neurodevelopmental disorder characterised by communication and social interaction limitations and consistent inflexible patterns of behaviour [2]. Prevalence estimates for both autism spectrum disorder and epilepsy are around 1 % [3]. However, nearly a fifth of people with autism will develop epilepsy by adulthood [4]. In this population there is an associated increase risk of premature mortality, morbidity and prevalence of other physical and psychiatric comorbidities [5].

The relationship between autism spectrum disorder and epilepsy is bidirectional, complex, undefined and in need of additional research [6]. This has thus led to complex treatment challenges [7]. Anti-Seizure Medications (ASM) are widely prescribed despite limited clinical trial data to demonstrate efficacy or tolerability in this population [8]. Prescribing guidance is limited [9]. Clinicians are advised to follow a cautious introduction and titration, whilst considering potential behavioral profile of certain ASMs where individuals have existing neuropsychiatric co-morbidities [9]. There may be greater susceptibility to adverse effects for people with autism because of challenges in communication, particularly relating to subjective symptoms [5].

Levetiracetam (LEV) is the most widely prescribed ASM in the UK, with comparable efficacy to other ASMs [10]. A second generation ASM, LEV has been found to generally have limited adverse effects, a favourable drug interaction profile and rapid titration potential [11]. Psychiatric and behavioral side effects have however been found to be significantly associated with LEV when compared to other ASMs [12].

Comprehensive and methodologically robust systematic review and data ratings supports LEV's use as a first-line ASM treatment in children with autism, which is well tolerated without detrimental behavioural or cognitive effects [13]. Furthermore, there has been reported improvements in such behaviors that challenge in small numbers of children who have autism prescribed LEV [14].

However, single centre audits and surveys dominate the review data, with controlled studies limited in scope and consistency of results [15,16], or with small numbers and non-seizure specific outcomes [13].

Specific neuropsychiatric and behavioural side effects (such as aggression) have been found to be a key factor in discontinuation of treatment in larger studies and surveys, particularly for those with intellectual disability [17,18].

Therefore, there is a need for more detailed treatment outcome data for LEV for people with autism, particularly understanding around LEV's impact on psychiatric and behavioural symptoms in this cohort. Comparing the response to LEV for people with autism and epilepsy and people with epilepsy who do not have autism, offers an opportunity to widen understanding around prescribing guidance for this specific epilepsy population.

In this paper we report on one arm of an existing Epilepsy, Intellectual Disability and/or Pervasive Development Disorders Research Database Register (Ep-ID Register), which has collected and analysed observational ASM data for over a decade comparing responses for people with and without ID/pervasive development [19,20].

Focus on more pragmatic observational methodologies regarding autism and epilepsy has been recently recommended [5], and this new Ep-ID arm, offers an opportunity for applying the existing methodology as a feasibility study for recruiting patients and analysing observational data evaluating ASM use for people with autism.

2. Material and methods

The data reported are from the Ep-ID Register, detailed in Appendix 1. The Ep-ID Register is an NHS ethics approved (24/SC/0221) Epilepsy Research Database Register. Ep-ID Data Collection Centres (UK NHS Trusts) contacted people (18+) who were currently or had previously

been prescribed LEV. Retrospective data were collected for a twelve-month period from when research participants were first prescribed LEV, with a standardised Ep-ID screening, recruitment (patient or carer consent) and data collection process employed. Demographics, clinical features, efficacy and tolerability (withdrawal and reason) data were collected. Side effects as identified by the British National Formulary were also collected and grouped into physical and mental health side-effects for analysis. Specific behavioral side-effects were also analysed. Improvement or worsening of seizures, (efficacy) were calculated using frequency of seizures recorded in patient records, or where explicit text detailed quantifiable percentage changes.

Baseline data, including non-identifiable demographic and diagnosis specific health data, were summarised by the mean and standard deviation (SD) for continuous variables (or median and inter quartile range (IQR) if the distribution was non-normal), and the number and percentage for categorical data. Normality of continuous variables was assessed using the Shapiro-Wilks test. Univariable associations between the Groups (autism and no autism), and the categorical demographic and baseline characteristics were assessed using Fisher's exact test. Univariable group comparisons of quantitative baseline characteristics were conducted with the Mann-Whitney test.

Univariable analysis of associations between autism group and the primary study outcomes (efficacy (at least 50 % improvement in seizure frequency), retention and risk of adverse effects at 12 months after initiating LEV treatment) were conducted with Fisher's exact test. 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 autism group differences after adjustment for potential confounders (age, gender, presence of baseline physical health and mental health conditions).

Seizure frequency (with categories 'worsening', 'no change', '≤25 % improvement', '25–50 % improvement', '>50 % improvement') was considered as a secondary outcome. Because Fisher's exact test does not account for the ordered nature of the seizure frequency variable, further univariable and multivariable testing for this outcome was conducted using an ordinal logistic regression model. The proportional odds assumption required for this model was tested using a Brant test [21]. Individual side-effects, including aggression and irritability, were analysed as exploratory outcomes.

Significance was accepted at $p < 0.05$. Results were interpreted with consideration of the hierarchical structure of outcomes (primary, secondary, exploratory) and without formal correction for multiple comparisons for the primary and secondary outcomes, acknowledging a higher Type I error risk in secondary analyses. For the exploratory analyses of associations between autism group and individual side-effects, we accounted for multiple testing separately amongst physical health and mental health side-effects by calculating adjusted p-values to control the false discovery rate using the Benjamini-Hochberg procedure. All analyses were performed using the R environment for statistical computing.

3. Results

The Sponsor site and 17 other English NHS Trusts (acting as Data Collection Centres) participated in this study, with recruitment of 49 people with autism and epilepsy and 228 people with epilepsy and no autism. LEV start date was not recorded for 37 participants and age was omitted for 1 participant. Their exclusion gave 40 participants with autism and 199 participants without autism.

All 40 participants with autism were aged 50 years or less, so a similar age restriction was applied to the non-autistic population to ensure comparability. This gave a final sample for analysis of 40 participants with autism and 135 without autism who have been prescribed LEV. The participants with autism included people with intellectual disability. The non-autism cohort did not include people with intellectual disability. Participants commenced LEV at a single point in a 20-

year period, between 2000 (UK licensing) and end of 2019/start of 2020.

Demographic and clinical features of research participants are detailed in Table 1. Just over half (52 %) of the study cohort were aged less than 30 years. Participants with autism were more likely to be in this younger age category (80 % compared to 43 %). Participants with autism were more likely to be male (68 %) than participants without autism (45 %). Mean starting dose of LEV was 645 mgs for the participants with autism compared to 612 mg for the participants without autism. Maximum mean dose of LEV was 1645 mg for participants with autism and 1658 mg for those without. No significant difference in baseline to three months (p = 0.427) or baseline to maximum dose (p = 0.563) titration was identified.

Comparative data for group association for efficacy, withdrawal and side-effects for participants with autism and those without autism is detailed in Table 2. A significant univariable association was evident between autism group and seizure improvement (efficacy) (Fisher's

Table 1
Demographics and clinical features of patients that underwent levetiracetam treatment.

	Overall (n = 175)	No ASD (n = 135)	ASD (n = 40)	P-value for group difference
Age (years)				
Median (IQR)	28 (19, 38)	32 (22, 41)	19 (15, 24)	<0.001
<18	29 (17 %)	13 (10 %)	16 (40 %)	<0.001
18–29	61 (35 %)	45 (33 %)	16 (40 %)	
30+	85 (49 %)	77 (57 %)	8 (20 %)	
Gender				
Male	88 (50 %)	61 (45 %)	27 (68 %)	0.019
Female	87 (50 %)	74 (55 %)	13 (33 %)	
Existing conditions				
Physical health				
Yes	98 (56 %)	75 (56 %)	23 (58 %)	0.858
No	77 (44 %)	60 (44 %)	17 (43 %)	
Mental health (non-psychotic)				
Yes	49 (28 %)	39 (29 %)	10 (25 %)	0.693
No	126 (72 %)	96 (71 %)	30 (75 %)	
Mental health (psychotic)				
Yes	10 (6 %)	7 (5 %)	3 (8 %)	0.698
No	165 (94 %)	128 (95 %)	37 (93 %)	
Intellectual Disability				
Yes	38 (22 %)	0 (0 %)	38 (95%)Mild 10 (25 %) Moderate/ Severe 28 (75 %)	<0.001
No	137 (78 %)	135 (100 %)	2 (5 %)	
Dose				
Starting dose (mg)Median (IQR)	500 (250, 688)	500 (250, 750)	500 (250, 500)	0.660
Maximum dose (mg)Median (IQR)	1250 (750, 2000)	1250 (1000, 2000)	1500 (750, 2000)	0.853
Titration comparison Baseline to 3 months				
Median (IQR)	500 (250, 1000)	500 (250, 875)	500 (250, 1000)	0.730
Titration comparison –Baseline to Max dose (p = 0.563)				
Median (IQR)	750 (250–1500)	750 (250–1500)	650 (250–1500)	0.968

Table 2

Univariable associations with autism group for efficacy, withdrawal and side-effects.

Efficacy P < 0.001 for association between autism and efficacy		
	No Autism	Autism present
Missing	18	7
Worsening	17 (14.5 %)	2 (6.1 %)
No change	35 (29.9 %)	8 (24.2 %)
25 % improvement	0 (0.0 %)	5 (15.2 %)
50 % improvement	12 (10.3 %)	8 (24.2 %)
75 %+ improvement	53 (45.3 %)	10 (30.3 %)
Withdrawal		
p = 0.626 for association between withdrawal rate and Autism		
	No Autism	Autism present
Missing	1	0
Yes	23 (17.2 %)	5 (12.5 %)
No	111 (82.8 %)	35 (87.5 %)
All Side-effects		
p = 0.165 and 0.791 for associations with physical and mental side-effects respectively		
	No Autism	Autism Present
Physical		
Yes	22 (16.3 %)	11 (27.5 %)
No	113 (83.7 %)	29 (72.5 %)
Mental		
Yes	21 (15.6 %)	7 (17.5 %)
No	114 (84.4 %)	33 (82.5 %)
Specific behavioral Side-effects		
p = 0.580 and 0.025 for associations with irritability and aggression respectively		
	No Autism	Autism present
Irritability	15 (11.1 %)	6 (15.0 %)
Aggression	2 (1.5 %)	4 (10.0 %)

exact test p < 0.001). However, the effect of autism group was not the same across all levels of seizure frequency (Brant test p = 0.03). Seizures > 50 % improvement was similar for the two groups (55.6 % non-autism, 54.5 % autism; Fisher's exact test p = 1.00). After adjustment for age, gender and baseline health conditions, no significant differences were found between autism group and likelihood of seizure improvement of >50 % (adjusted OR = 0.81, 95 % CI = 0.33–1.95, p = 0.633).

Withdrawal rates were slightly lower for participants with autism (12.5 % compared to 17.2 %), but the association was not statistically significant in unadjusted analysis (Table 2; p = 0.626). Similar findings were obtained in multivariable analysis, after adjustment for age, gender and baseline health conditions (adjusted OR for withdrawal in autism group compared to non-autism group = 0.72, 95 % CI = 0.21–2.12, p = 0.569).

Participants with autism had a slightly higher prevalence of physical and mental side effects, but no significant association was identified in univariable analysis (Table 2; physical, p = 0.165, mental health, p = 0.791). After adjustment for age, gender and baseline health conditions, no significant differences were found between autism group for physical (adjusted OR = 1.71, 95 % CI = 0.65–4.38, p = 0.268) or mental side-effects (adjusted OR = 0.91, 95 % CI = 0.30–2.52, p = 0.856). There was a significant univariable association with autism group for aggression (p = 0.025) but not irritability (p = 0.580). However, the numbers reporting 'aggression' were small (n = 4 with autism, n = 2 without autism) and the association was no longer significant after adjustment for multiple testing across the 5 mental health side-effects (p = 0.126). Furthermore, aggression was not associated with autism group after adjustment for age, gender and baseline health (adjusted OR = 3.66, 95 % CI = 0.61–29.8, p = 0.171).

4. Discussion

This study provides the first retrospective, real-world, observational study where adults with autism and epilepsy who have been prescribed LEV are compared to adults with epilepsy without autism. Findings add to the limited trial data reported for children and adolescents prescribed LEV [16]. This study provides real world adult ASM efficacy data, absent from previous survey studies, or those with small sample sizes only powered to study feasibility and tolerability [8,15].

Those with autism who were recruited to our study responded in a non-linear fashion as compared for efficacy (>50 % improvement in seizure frequency). Analysis of group associations did however find a non-linear association ($p < 0.001$) for research participants with autism and seizure frequency. This indicates that whilst both populations in our study have similar rates of >50 % improvement, participants with autism were less likely than those without autism to have a '75 %+ improvement', 'no change' or 'worsening' of seizures.

The limited evidence base for people with autism has driven recommendations for a cautious introduction and titration of ASMs [9]. The similar response to LEV for participants with and without autism in our dataset are however from cohorts with similar starting dose, end dose, and titration rates. There was no association between physical and mental health side effects and autism. Although the data did suggest that 'aggression' was associated with the participants with autism, this association was no longer significant after adjustment for multiple testing or potential confounders. It is not known if the potential negative behavioral profile of LEV was considered before deciding to prescribe LEV for participants in this study. Numbers were however small ($n = 4$) but it is also not known if the potential negative behavioral profile of LEV was considered before deciding prescribing LEV for participants in this study. This should be considered alongside recommendations for cautious introduction and titration for LEV.

5. Limitations

It is important to note the large number of research participants with autism in our dataset who also had intellectual disability (95 %). Our cohort is therefore primarily representative of autistic people with intellectual disability and not "able autism". Larger numbers would be required to study this specific population.

The number of concomitant ASMs were not recorded for all participants and therefore not included in analysis. The potential confounding effect of additional ASMs is therefore not known.

One challenge for such larger-scale and multi-centred studies is the quality of clinical data recorded and categorised in medical records. Key diagnosis requiring referral for specialist support are for example clearly identifiable in electronic health care record systems, but other diagnoses such as autism are often poorly recorded [22]. A lack of standardisation of electronic health care record systems used by the NHS compounds this problem.

There were methodological limitations with this feasibility study. An inability to identify patients with an autism specific diagnosis prior to recruitment resulted in a small number of participants with autism, restricting the power to detect group differences. Identification of diagnosis pre-recruitment may have enabled sampling to ensure fewer people with no autism were contacted. However scoping work at six DCCs indicated that autism diagnosis was not possible to extract through existing medical record systems without researchers manually processing data. With autism diagnosis not recorded explicitly in diagnostic sections of medical records, researchers were required to mine progress notes and patients' clinical letters in electronic records post consent. With autism not recorded routinely or explicitly in medical records it should not be discounted that there could be some research participants in the general population who were also autistic.

The modifications and challenges for electronic systems to allow for such specific diagnostic screening and extraction work have been

highlighted [23]. Medical records systems and Information technology are evolving. Epilepsy researchers are for example developing natural language processing technology for facilitating the extracting of such data [24]. Such technology would make future identification and extraction of specific patient diagnostic data possible without researchers processing data manually, allowing for similar studies to be completed with the Ep-ID research register methodology more efficiently.

6. Conclusion

This study supports the use of LEV for autistic people with epilepsy as there is no difference in response noted to those without autism.

7. Data statement

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

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.

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.

CRedit authorship contribution statement

Jon Allard: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **William Henley:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Brendan McLean:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Lance Watkins:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Formal analysis. **Mary Parrett:** Writing – review & editing, Visualization, Validation, Resources, Data curation. **Sanjeev Rajakulendran:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Data curation. **Melissa Maguire:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Data curation. **Shan Ellawela:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Data curation. **Phil Tittensor:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Data curation. **Juliet Bransgrove:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Data curation. **Arjune Sen:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Data curation. **Rajiv Mohanraj:** Writing – review & editing, Visualization, Validation, Supervision, Data curation. **Many Bagary:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Data curation. **Sunil Ram:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Data curation. **Sarah Pashley:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Data curation. **Rohit Shankar:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration,

Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Autistica 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 and the Oxford Research Group have received institutional and research support from Bial, Eisai, Livanova, UCB Pharma. RS and his research group has received Honoraria, institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Angelini, UnEEG and Jazz/GW pharma outside the submitted work. RS 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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Appendix 1

'A register for collecting and measuring outcomes of licensed Anti-Epileptic Drugs and other Treatments in patients with Epilepsy and Intellectual Disability and/or Pervasive Development Disorder' (Ep-ID Register)

<https://www.plymouth.ac.uk/research/cider-cornwall-intellectual-disability-equitable-research>.

The Ep-ID Register is an NHS ethically approved (24/SC/0221) Epilepsy Research Database Register. The Register is hosted at the Cornwall Intellectual Disability Research (CIDER) Centre, a partnership between Cornwall Partnership NHS Foundation Trust and the University of Plymouth focussing on people with intellectual disability. The Ep-ID Register employs a non-interventional observational method for collecting pre-existing retrospective data recorded in NHS patients' medical records. English NHS Trusts who collaborate with Ep-ID act as Data Collection Centres (DCCs). Protocolised methods for recruitment, data collection and data analysis are employed. Previous studies have compared response to ASMs for patients with and without ID. In 2019 Ep-ID was extended and ethically amended to study specific epilepsy populations and treatments.

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