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Perampanel in the general population and in people with intellectual disability: Differing responses

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ABSTRACT

Purpose: There is a shortfall of suitably powered studies to provide evidence for safe prescribing of AEDs to people with Intellectual Disability (ID). We report clinically useful information on differences in response to Perampanel (PER) adjunctive treatment for refractory epilepsy between ID sub-groups and general population from the UK Ep-ID Research Register.

Method: Pooled retrospective case notes data of consented people with epilepsy (PWE) prescribed PER from 6 UK centres was classified as per WHO guidance into groups of moderate -profound ID, mild ID and General population. Demographics, concomitant AEDs, starting and maximum dosage, exposure length, adverse effects, dropout rates, seizure type and frequency were collected. Group differences were reported as odds ratios estimated from univariable logistic regression models.

Results: Of the 144 PWE (General population 71, Mild ID 48, Moderate to profound ID 48) examined the association between withdrawal and ID type was marginally statistically significant ($p = 0.07$). Moderate to profound ID PWE were less likely to come off PER compared to mild ID (OR = 0.19, CI = 0.04–0.92, $p = 0.04$). Differences in mental health side effects by groups was marginally statistically significant ($p = 0.06$). Over 50% seizure improvement was seen in 11% of General population, 24% mild ID and 26% Moderate to profound ID.

Conclusions: PER seems safe in PWE with ID. It is better tolerated by PWE with Moderate to profound ID than PWE with higher functioning. Caution is advised when history of mental health problems is present. The standardised approach of the Ep-ID register UK used confirms that responses to AEDs by different ID groups vary between themselves and General population.

1. Background

Intellectual Disability (ID) is the incomplete development of cognition and is characterized by impairment of skills manifested during the developmental period, which contribute to the overall level of intelligence, i.e. cognitive, language, motor, and social abilities [1]. Levels of severity of ID are stratified into mild (IQ of 50–69), moderate (35–49), severe (20–34), and profound (<20) [1]. Amongst those with ID about 85% have a mild condition, 10% moderate, 4% severe and about 2% profound ID [2].

Life expectancy is reduced in people with moderate or higher degree of ID with standardized mortality rates of around 3 [3]. There is also higher mental health [4] and physical comorbidity [5] in ID populations as compared to the general population.

Epilepsy and ID are associated with a range of pathological processes [6]. The prevalence of epilepsy in people with ID is

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around 22% [7] and rises with increasing severity of ID [8]. For mild ID it is around 10% compared to 30% to moderate to profound ID [9]. Most people with ID and epilepsy respond poorly to anti-epileptic medications as compared to the general population [8]. Epilepsy in people with ID is associated with increased psychological and behavioural problems [10], healthcare costs [11], morbidity [12] and mortality [13] relative to non-ID population. There are higher rates of side effects [14] and polypharmacy [15] in the ID population. In England, people with ID are 5 times more likely to have a potentially avoidable emergency admission to hospital [16]. Epileptic seizures are the most frequent factor accounting for approximately 6000 admissions a year, equivalent to 40% of all avoidable emergency admissions in adults with ID [16]. As Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment to prevent avoidable harm in this vulnerable group it is important to ascertain the most appropriate and relevant drug therapies for this group. There is currently little evidence to inform on prescribing AEDs in people with epilepsy and ID [17].

Perampanel (PER) is licensed for use as an adjuvant in refractory focal epilepsy [18,19]. A recent study [20] in people with ID has shown behavioural side effects were present in 40.3%. Based on dose related side effects such as aggression seen in 1–3% and irritability 4–12% of people it has been suggested that its use in people with psychiatric conditions, behavioural problems and ID be considered cautiously [19].

A multicentre study [21] adults with refractory epilepsy prescribed PER with a subgroup analysis of people with ID showed no difference in dropout rates and efficacy to general population and noted similar side effects including psychiatric and behavioural issues. Differences were noted in titration speeds in the two populations. This study however did not, define 'ID', validate the ID diagnosis or stratify people into recognized subgroups. This is important given the clinical differences in presentation of those with mild versus moderate to profound ID as this would help define better person centred treatment in this population.

The UK Ep ID Research Register [17] was created in 2015 to collect data on efficacy and safety in people with epilepsy and ID compared to individuals with IQ >70 for newer AED (licensed after 1999). Those with ID are divided into 2 groups i.e. mild ID and 'moderate to profound ID' based on the rationale in Appendix 1 in Supplementary Material. The Register has Ethics Approval (reference: 14/SC/1270) for data collection and is National Institute of Health Research (NIHR) UK adopted with seven UK sites currently affiliated and recruiting. The Register is modelled after the UK Epilepsy and Pregnancy Register that was created for women of childbearing age who have epilepsy and has provided valuable longitudinal results on the effects of AEDs in a little studied population. Similarly people with ID form a significant minority in both epilepsy populations in general and treatment resistant populations in particular they are not included for any systematic trails when a molecule is licensed. Any prescribing issues are by personal experience, peer feedback and imposition of evidence from general population. To address this gap and provide better quality real world prescribing guidance the Ep-ID Research Register was formed. The UK Ep-ID Register has 10 years ethics and similar to the current study on PER would look longitudinally at outcomes of other commonly used AED molecules in due course.

2. Methods

Data was obtained from 6 sites. All adults prescribed PER at the sites at any point (current or withdrawn) prior to 03/2015 and having had at least 1 follow up post PER commencement were sent a letter by their attending physician requesting consent to be contacted. Those who agreed were then contacted by a researcher who went through the informed consent process. For those with ID, the consenting process included providing 'easy read' study information and specially developed consent forms. When one was deemed not able to provide informed consent a family member or a carer could assent. Those on treatment for less than a year or on monotherapy were excluded. All participants were from the community who attended outpatients at their respective centres. Where a patient dropped out due to side effects prior the first follow up the contact made to notify was accepted as the 'follow up'.

Data was obtained for those consenting or had assented by reviewing case notes and these were recorded. Case notes were reviewed for a period of up to 15 months starting with 3 months prior to commencement (baseline), 3 months post commencement and then 6 months and 12 months. Endpoint was defined as either 1 year if the individual continued with PER treatment or when the drug was withdrawn. Withdrawal rates of PER were estimated as the proportion of people who discontinued PER within the first year.

Demographics data, seizure type, concomitant AEDs, starting and maximum dosage of PER, length of exposure, adverse effects, dropout rates and seizure frequency were collected. Duration of epilepsy was ascertained in intervals of 5 years. Seizure frequency was recorded as monthly numbers but consolidated into% improvement from baseline in blocks of 3 months and results between baseline and endpoint compared.

Outcomes following treatment were defined as worsening or no improvement, greater than 25%, 50%, 75% improvement in seizures based on the difference in seizures at endpoint compared to baseline. Seizure freedom was terminal remission at end point.

No reduction or seizure aggravation was based either on numerically recorded frequencies or on clinical impression.

Participant's health profile was requested from their primary care physician or a discussion took place with a professional at the practice to collect relevant information to classify ID. All primary care practices in the UK are expected to have a record of patients who have been 'statemented' or have a diagnosis of Learning or Intellectual disability as it is a NHS Employers Quality Outcome Framework factor identified as "The contractor establishes and maintains a register of patients with learning disabilities". The health profile also contains a list of nature and degree of ID, co-morbidities, mental and physical deficits. Where identified pre-existing conditions were divided into mental and physical co-morbidity. Major mental health conditions recorded on the profile were counted. These included Depression (including suicidal ideation), Anxiety, Psychosis, Pervasive Developmental Disorders such as Autism, Attention Deficit Hyperactivity Disorder etc. Medical conditions were predominantly pre-existing chronic conditions such as neuromuscular disorders such as cerebral palsy, metabolic syndromes such as diabetes, respiratory issues such as Chronic Obstructive Pulmonary Disease, Asthma and other neurological conditions such as stroke. Where the degree of ID was not specified two ID specialists reviewed the profile independently and identified best fit. No conflict was found in classifying ID into the two groups. Those not on the primary care ID Register was considered suitable for the 'general' group.

Analysis was undertaken a year after the cut-off date to give full opportunity for all to have had a year of PER. Fisher's exact test was used to test for univariate associations between outcomes (withdrawal, efficacy, adverse events) and ID group (normal/mild ID/moderate to profound ID). Differences between ID groups were reported as odds ratios estimated from univariable logistic regression models. Age and gender were added to these models as explanatory factors and the results reported if the adjusted model provided a better fit to the data. The threshold for statistical significance was $p = 0.05$. Associations with $0.05 \leq p < 0.1$ were reported as marginally statistically significant.

2.1. Power

The sample size of n = 71 patients without ID and n = 25 patients with moderate to profound ID provides 80% power at a significance level of 5% to detect a group difference in drop-out rates of 30%, assuming a rate of 50% in the non-ID group. Although the study was adequately powered to detect large effect sizes, difficulties in recruiting sufficient patients with moderate to profound ID meant that the study was underpowered to detect small to moderate effect sizes that could still have clinical implications. By pooling together all ID patients, the study would be powered to detect a smaller difference in drop out rates of 23%.

3. Results

Of the 279 people originally approached 259 responded of whom 152 were fully consented and 144 found eligible. Eight did not satisfy criteria and were excluded. A significant proportion of the remaining 107 when contacted were willing to participate but did not post back the signed consent forms even when reminded.

There are 71 people from general population (37 females), 48 with Mild ID (26 females) and 25 with moderate to profound ID (16 males). Age ranged between 20 and 76 years old (mean 44), with Mild ID 23–76 years (mean 48) and the moderate -profound ID 24–63 years (mean 39). Chronic medical conditions were present in 34% and concurrent mental health problems in 13%. Table 1 provides group specific baseline clinical data including seizure frequencies by sub groups.

Ninety nine participants of the 144 had epilepsy for over 15 years including 50/71 of general population, 34/48 in Mild and 15/25 in moderate to profound groups (Fig. 1). Mean number of concomitant AEDs was 2.8 for general population, 3.8 for mild ID and 4.1 for moderate to profound ID.

The starting dose of PER was 2 mg per day in all cases. Doses were compared after the initial 3 month period of commencement and at the endpoint (Table 2). At 3 month, 69% of the general population had higher than 2 mg/day doses (mean dose 4.89 mg/day after 3 months of commencement, median 4.5 mg/d) but only 36% and 39% of the mild and moderate to profound groups (mean doses for both groups 3.3 mg/day and median doses 2 mg/d after 3 months of commencement) had moved to a higher dose. The general group had a total mean dose of 6.63 mg/day versus 5.82 mg/day for mild ID and 4.96 mg/day for moderate to profound ID. Median final doses were 6, 6 and 4 mg/day for general, mild and moderate to profound groups respectively. The mean increases in doses from starting to endpoint in the period of exposure of up to 1 year or drop out were 2.52 mg/day in the mild ID group compared to general 1.84 mg/day and moderate to profound of 1.65 mg/day. The median increases were 2 mg/d in all 3 groups.

Table 1
Clinical features of patients that underwent PER treatment and study group.

	Number (%)	No ID	Mild	Moderate to profound
Age				
<40	54 (38%)	21	21	12
40–60	68 (47%)	34	23	11
60+	20 (14%)	16	3	1
Missing data	2 (1%)	0	1	1
Sex				
Male	72 (50%)	34	22	16
Female	71 (50%)	37	26	9
Missing data	0	0	0	0
Chronic medical condition				
Yes	92 (64%)	46	30	16
No	47 (33%)	25	13	9
Missing data	5 (3%)	0	5	0
Mental health comorbidity (other than ID)				
Yes	19 (13%)	8	10	1
No	125 (87%)	63	38	24
Missing data	0	0	0	0
Seizure Types				
Generalised	68	27 (38%	27 (56%)	14 (56%)
Focal	73	41 (58%)	21 (44%)	11 (44%)
Both	3	3 (4%)	0	0

The association between withdrawal and ID type was marginally statistically significant (Table 2, p = 0.07, Fisher's exact test). People with moderate to profound ID were less likely to come off PER compared to patients with mild ID (OR = 0.19, CI = 0.04–0.92, p = 0.04). There was no difference in withdrawal rates between the general population and patients with mild ID (p = 0.25).

All adverse events (AEs) were divided into mental and physical health sets for each subgroup (Table 2). All AEs were populated as identified specific to PER. There was marginally statistically significant evidence of differences in mental health side effects by ID group (p = 0.06, Fisher's exact test) but no such differences were seen for physical side-effects (p = 0.33, Fisher's exact test). The risk of mental health side effects was increased in the moderate to profound ID group relative to the general population with epilepsy (OR = 4.2, CI = 1.1–15.2, p = 0.03) but not in the mild ID group relative to the general population (OR = 2.6, CI = 0.8–8.6, p = 0.11). The number of recorded AEs in each group was similar (Table 3). There were reported AEs of 32% in the group without ID, 33% in those with mild ID, and 28% in those with moderate to Profound ID. When combining the general population and ID groups, there was a univariate association between a history of co-morbid mental health/behavioural condition and being more likely to encounter mental health/behavioural side effects (Table 4, p = 0.02, Fisher's exact test). The specific psychological side effects observed were challenging behaviour in the form of an occurrence or increase in aggressive, agitated, disruptive behaviour, depression, anxiety, mood swings and confusion.

Behavioural/mental health problems across the age there was a seven fold increase in risk in patients aged less than 30 years of age relative to patients aged 30 or more (OR = 7.2, CI = 1.5–34.7, p = 0.01). The main reason for withdrawal in all groups was intolerable side effects (50- 60%). Psychological side effects dominated the reasons for withdrawal in the ID groups. Lack of efficacy led to 20% of withdrawal in the Mild ID group. These and other factors for all 3 groups are presented in Tables 2 and 3.

None was seizure free. Greater than 50% seizure improvement was seen in 11% of general population, 24% with mild ID and 26% with moderate to profound ID (Tables 2 and 3). These differences were not statistically significant (p = 0.11, Fisher's exact test). No improvement was noted in 79% of general, 53% of mild ID and 48% of moderate to profound ID. One person in group had seizure aggravation.

4. Discussion

We present a pragmatic real world observational survey of PER retention in a cohort of people with and without ID. The strengths include robust case selection and defined ID criteria. People with ID, their families and carers seem more amenable to participate in research especially into conditions where ID is involved possibly due to paucity of evidence and previous opportunities. This is highlighted by our high uptake of people with ID. There are several observations of interest.

Firstly, there are differences between people with mild ID and moderate to profound ID in terms of drop-out rates and efficacy, although these did not reach definite statistically significance.

Secondly, it appears fewer people with moderate to profound ID stopped PER even though similar side effect rates were reported. This may be because some side effects (such as dizziness) were not detected due to the communication problems these people

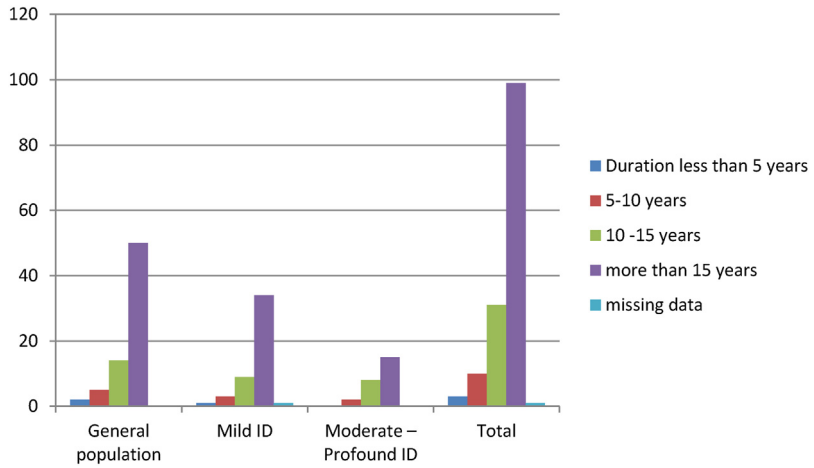

Fig. 1. Duration of Seizures in relation to individual groups.

Table 2
Outcomes of the study.

	All participants	No ID	Mild ID	Moderate to profound ID
Maximum dose achieved at 3 months and overall titration profile				
2 mg	64 (44%)	22 (31%)	28 (58%)	14 (56%)
>2 mg	73 (51%)	48 (68%)	16 (33%)	9 (36%)
Missing data	7 (5%)	1 (1%)	4 (8%)	2 (8%)
Mean dose 1st 3 months	4.1	4.89	3.30	3.30
Mean max dose		6.63	5.82	4.96
range	2–12	2–12	2 –10	2–10
Dropout rates				
Yes	32 (23%)	15 (21%)	15 (31%)	2 (8%)
No	110 (77%)	54 (76%)	33 (69%)	23 (92%)
Missing data	2 (0%)	2 (3%)	0	0
Frequency of physical side effects				
Yes	39	19 (27%)	16 (33%)	4 (16%)
No	105	52 (73%)	32 (67%)	21 (84%)
Frequency of mental side effects				
Yes	19	5 (7%)	8 (17%)	6 (24%)
No	125	66 (93%)	40 (83%)	19 (76%)
Reasons identified for coming off PER				
Increased seizure frequency	7	4	2	1
Intolerable side-effects	18	8	9	1
Lack of efficacy	3	0	3	0
Other	4	3	1	0
Increased seizure frequency	7	4	2	1
Efficacy				
No change	90 (63%)	55 (79%)	24 (53%)	11 (48%)
25% improvement	21 (15%)	6 (9%)	9 (20%)	6 (26%)
50% improvement	20 (14%)	6 (9%)	9 (20%)	5 (22%)
75% improvement	5 (3%)	2 (2%)	2 (4%)	1 (4%)
Worsening	2 (1%)	1 (1%)	1 (2%)	0 (0%)
Missing data	6 (4%)	1	3	2

Table 3
Summary of efficacy and tolerability data for treatment with PER by ID group.

	Responder rate (>50% reduction in seizures)	Retention rate at 1 year	Adverse events
Overall	18%	77%	All AEs = 32% Dizziness = 7.6% Memory problems = 6.9% Increased seizures = 6.9% Confusion = 4.2% Behavioural disturbance = 3.5% Sedation = 3.5%
No ID	11%	78%	All AEs = 32%
Mild ID	24%	69%	All AEs = 33%
Moderate to profound ID	26%	92%	All AEs = 28%

Table 4
Association of mental health condition history and mental health side effects to PER.

History of comorbid mental health conditions	Mental health side-effects	
	Yes	No
Yes	6 (32%)	13 (68%)
No	13 (10%)	112 (90%)

encounter, or some side effects do not seem to impact on this group. There was a greater drop-out in people with mild ID. Side effects were similar to the comparison groups, but it may be that known side effects of PER, are less tolerated in this group. The 'mild ID' population is vulnerable to a high degree of suggestibility and known to present with more 'attention seeking health conditions' [22]. This might have resulted in a lower threshold to report effects compared to the general population and those with more profound ID, although this remains a speculation. Attention to the way communication of side effects is undertaken and how it is explored when concerns arise in this group may help clarify this.

Thirdly, slower titration as shown in the moderate -profound ID population appears to facilitate better retention of medication and our study suggests that outcomes were better with treatment persistence.

While it's likely that minor side effects go unnoticed or non-communicated in the moderate to profound population it raises the issue of whether people with epilepsy or their family reporting minor side effects and wishing the AED to be withdrawn are counselled of the potential harm of losing a viable therapeutic option. Stopping drugs need to be deliberated in context of the increased risk of premature mortality in people with treatment resistant epilepsy [23,24]. Person centred and flexible strategies with the individual as the partner may pay dividends in helping better retention. This includes considering slower titration of medication [25], reducing to the previous suitable dose and medication management education.

We compared our findings to two recent PER studies [19,20,21]. Our overall findings co-relate to the findings of these studies. Two of the studies [20] examined the effects of PER in a subpopulation of ID. One study [21], however, made no distinction between mild and moderate to profound levels of ID and drop-out rates after 12 months were far higher at 62% for ID and 52% for non-ID groups. Efficacy was much better for both groups at 43% having more than 50% improvement in seizure frequency. A recent study [20] which specifically looking at populations if ID did not compare with general population. Their ID sample was less to our ID sample size but comparable. The seizure reduction rates of around 50%, better retention rates by more severe ID patients and the dosing were comparable to our study results.

Our observations suggest that PER seems safe in people with ID. It appears to be better tolerated by people with moderate to profound ID than in people with higher functioning, although this might be due to communication difficulties. Moderate -profound group efficacy may be superior to the other 2 groups, whether due to persistence in use or inherent better efficacy.

PER should be used with caution and care in people who has a past history of mental health problems and behaviour disturbances particularly if under the age of 30 years.

We acknowledge several limitations. Firstly, people were retrospectively consented, which might introduce a bias towards people with a more favourable response. Seizure frequency and side effects data were retrospectively collected from medical notes and might thus introduce bias towards the most recent experience of the person or their caregiver. The numbers in our treatment groups may also introduce a type 2 error of not finding statistical differences when they may be present. Although the study did yield some interesting findings we view our findings as provisional and requiring replication before mandating a change in clinical practice because of the borderline statistical significance and the potential for bias in retrospective analysis of case notes. Further the study has not looked into the number of con-commitment medication, daily dosing and dose dependency influences on side effects.

The study uses a standardised approach of the Ep-ID register UK. It confirms our hypothesis that the response to AEDs of people of different ID groups varies between themselves and the general population.

Conflict of interests

WH, CW, MM, ZD and RL report no conflicts. RS and BMcL have received institutional, research support and personal fees from Eisai, Bial, UCB, Desitin and Special Products Ltd. AP, MM and MS have received research support and personal fees from Eisai and UCB outside the submitted work. JWS has received grants from Eisai, GSK and UCB and personal fees from Eisai, UCB, Lundbeck and Teva, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2017.05.012.

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