



# European perspective of perampanel response in people with Intellectual Disability

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## Abstract

**Background:** Epilepsy prevalence is over 20% for those with ID. It is difficult to diagnose and treat and more likely to be treatment resistant. The evidence informing prescribing is sparse, particularly for new drugs such as perampanel (PMP).

**Aims of the Study:** This study seeks to strengthen the research evidence regarding PMP for people with ID by pooling information from two isolated and separately conducted studies: the UK-based Epilepsy Database Register (Ep-ID) and the data from the Kempenhaeghe clinic in the Netherlands.

**Methods:** A single data set of comparable data was created and analysed under agreement and supervision of a UK statistician.

**Results:** Seizure reduction within twelve months was evident in 62% of Dutch and 47% of UK patients. Retention rates were higher for those in the UK ( $P = .01$ ) and for patients with moderate to profound ID, whilst side effects were more prominent in the Dutch cohort.

**Conclusions:** Comparable rates of seizure reduction are in line with estimates for non-ID patients, adding to the evidence suggesting that PMP has a similar impact on those with ID. Taking a European perspective and sharing data across centres can help strengthen the evidence for prescribing antiepileptic drugs in the ID population.

## KEYWORDS

behavioural health, co morbidity, Epilepsy, Intellectual disability, mental health, perampanel, physical health, seizures, UK Ep-ID Database Register

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## 1 | BACKGROUND

Epilepsy is a common health problem among people with an intellectual disability (ID), with prevalence estimated around 22.2% and rates increasing with severity of ID.<sup>1</sup> This is substantially higher than the reported prevalence of 1% in the general European population.<sup>2</sup> Epilepsy in the ID population is often more difficult to diagnose and treat, requires polypharmacy in many cases and is more likely to be treatment resistant.<sup>3,4</sup> As antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment for preventing avoidable harm, it is important to ascertain the most relevant and appropriate medications. AEDs with new modes of action have been introduced in recent years, but patients with ID are usually excluded from the initial registration studies, due to both ethical and practical reasons. There is therefore limited evidence to inform AED prescribing in people with epilepsy and ID.<sup>4,5</sup>

Perampanel (PMP), is a non-competitive  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist. PMP was accepted in 2012 as an add-on AED for focal-onset seizures in patients aged twelve years or above by the European Medicines Agency (EMA). Initial registration studies were followed by observational studies focussing on clinical experience, which confirmed the efficacy and safety of PMP in people with refractory epilepsy.<sup>6-8</sup>

Evidence regarding the clinical experience of PMP in people with ID and epilepsy is limited. A multicentre retrospective case note review UK study, which included a sub-group of people with ID (86 of the total 310 patients), showed no difference in dropout rates, efficacy and side effects from the general population.<sup>9</sup> Another retrospective UK study compared mild and moderate-severe ID populations with those who have epilepsy from the general population (also through medical records review) and reported findings supporting the safe use of PMP for those with ID, along with indicators of higher tolerability and efficacy for those with moderate to profound ID compared to mild ID.<sup>10</sup> Behavioural side effects were however cited in the 73 ID patients (from the total cohort of 144) particularly in those with a previous history of mental health or behavioural concerns, and this was also apparent in two additional European studies,<sup>11,12</sup> with a Dutch study reporting side effects in 40.3% of 62 ID patients<sup>11</sup> and a German study of 27 patients suggesting caution should be considered for PMP use in those with ID and known psychiatric conditions or behavioural problems.<sup>12</sup> Both the Dutch and German studies focused exclusively on ID populations. The growing evidence base is however small, and more in-depth clinical guidance for this vulnerable population is required.<sup>13,14</sup>

## 2 | AIMS OF THE STUDY

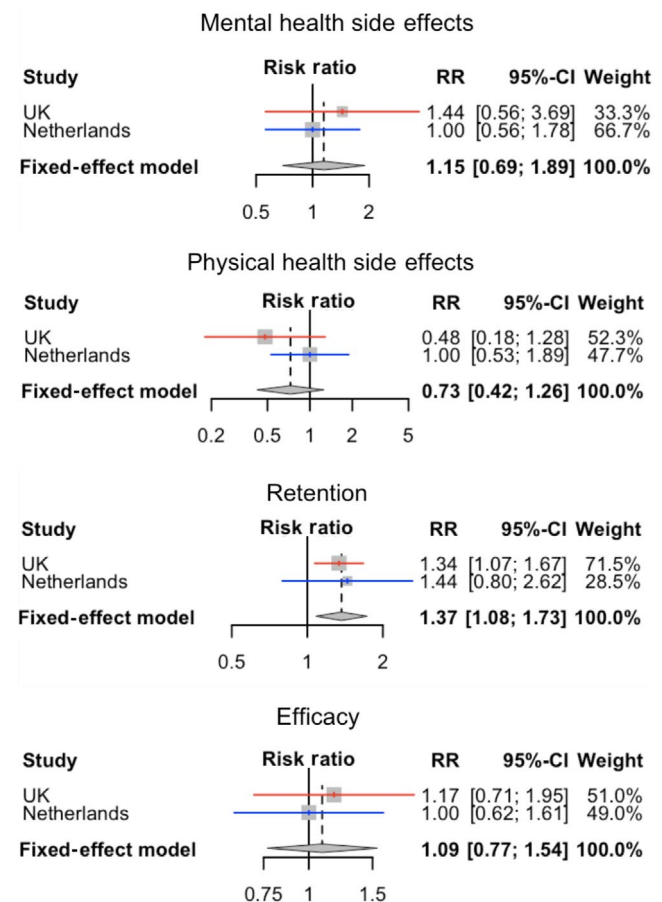
To build the research evidence regarding the use of PMP in people with ID, by pooling and comparing data sets from two of the European studies detailed above.

## 3 | METHODS

A UK and Dutch collaboration has been set up to draw findings from the UK-based Epilepsy Database Register (Ep-ID)<sup>10</sup> and the data from the Kempenhaeghe clinic, a tertiary epilepsy centre.<sup>11</sup> The paper also looks to provide insight into the possibilities for such cross-national work.

Data collected, recruitment processes and research methodologies employed for both the UK and Dutch studies, are detailed in Supporting Information S1. Work was completed to synchronize the two data sets (Supporting Information S1). A single data set of comparable data was then created. This detailed 12 months of clinically recorded data relating to the use of PER in both patient populations. An expert UK statistician (WH) ensured suitable homogenization of the data set to allow appropriate and direct comparison of the two cohorts. It also allowed for certain data to be pooled and analysed. All data remained confidential and anonymous. Both data sets at time of collection had relevant ethics approvals.

Adverse effects, dropout rates, seizure type and frequency were estimated separately for the UK, Dutch cohorts and for the combined data. Comparisons of outcomes in the mild and moderate to



**FIGURE 1** Forest plots showing risk ratios (RR) for differences in retention, efficacy and side effects between mild and moderate to profound ID. RRs of greater than 1 indicate a higher risk of the outcome for moderate to profound ID. Pooled estimates are shown based on a fixed-effects model

profound ID groups were made using fixed and random effects meta-analysis in the R software environment for statistical computing (with the 'meta' package). Heterogeneity between studies was assessed using the  $I^2$  statistic. Comparisons of overall outcome rates in the UK and Dutch data were made using Fisher's exact test.

The homogenization ensures wherever possible that the inclusion/exclusion criteria for the two populations were comparable and that the variables in the two data sets had consistent definitions, with measurements taken at the same time points such as having consistency in the population examined and the diagnosis. Details are given in Supporting Information S1.

Analysis is presented for the individual studies to allow comparisons with the results from the original papers and to highlight differences between the studies. The method of pooling used for the analysis was a fixed effects meta-analysis.<sup>15</sup> This assumes the underlying effect is the same in the two studies, and the observed effects differ because of sampling variation. The random effects model assumes each study estimates a different underlying true effect, and these effects have a distribution. There is expected considerable heterogeneity between these two separately conducted studies in terms of demographic and clinical characteristics. The  $I^2$  statistic is a measure of how much heterogeneity there is between studies with values close to 0% indicating low heterogeneity and values of over 75% corresponding to high heterogeneity. All analyses were conducted using the statistical software R.

## 4 | RESULTS

The aim of this study was to explore whether there was potential for pooling information from the studies. Pooled response data are presented in Table 2 for descriptive purposes. Further analysis revealed little evidence of study heterogeneity when comparing responses across ID sub-groups (indicated by the low  $I^2$  values in Table 3). For this

**TABLE 1** Demographic and clinical data

	UK Study	Dutch Study
Age	Mean = 43.3 y SD = 14.7	Mean = 36.2 y SD = 13.7
Age at onset	Mean = 12.3 y	Mean age at onset = 7.4 y
Sex	Male—38 (52%) Female—35 (48%)	Male—28 (67%) Female—14 (33%)
ID type	Mild—48 (66%) Mod/Prof—25 (34%)	Mild—21 (50%) Mod/Prof—21 (50%)
Seizure/Epilepsy type	Generalized—41 (56%) Focal—32 (44%)	Generalized—9 (21%) Focal—33 (79%)
Medication dosage and titration	Starting dose 2 mg Mean Max—5.82 mg	Starting dose adult—2 mg Mean Max 6.5 mg

reason, it was decided to present a formal pooled analysis of ID subgroup differences in retention, efficacy and side effects in Figure 1.

### 4.1 | Demographics and clinical data

Patient demographics and key clinical data from both studies are detailed in Table 1. Study heterogeneity was identified from the demographic and clinical data. Variations in the age of participants (UK mean 43.3 years vs Dutch mean 36.2 years) and sex (UK females 48% vs 33%) were apparent. More of the UK cohort had mild ID (66%), compared to a 50% split in the Dutch group. Seizures types were different with UK Generalized 56%, Focal 44% compared to Dutch 25.8% and 74.2%

Starting dose was 2 mg for adult patients in both cohorts. Maximum dosage used for patients was similar (UK 5.82 mg and Dutch 5.6 mg).

There were also differences in seizure type with 56% of UK patients but only 21% of Dutch patients having seizures defined as "generalized."

### 4.2 | Response to perampanel

Twelve month summative data regarding efficacy, tolerance, retention and side effects associated with PMP for UK and Dutch patients

**TABLE 2** Response to perampanel

	UK study	Dutch study	Pooled data
Overall			
Sample size, n	73	42	115
Seizure reduction	47%	62%	53%
Retention	77%	52%	68%
Side effects			
Mental health	19%	52%	31%
Physical health	27%	48%	35%
Mild ID			
Sample size, n	48	21	69
Responder rate	44%	62%	50%
Retention	69%	43%	61%
Side effects			
Mental health	17%	52%	28%
Physical health	33%	48%	38%
Moderate to profound ID			
Sample size, n	25	21	46
Responder rate	52%	62%	57%
Retention	92%	62%	78%
Side effects			
Mental health	24%	52%	37%
Physical health	16%	48%	30%

Outcome	Heterogeneity ( $I^2$ ) for comparison of ID groups	Test for difference in outcome rates between studies (UK vs Dutch data)
Efficacy	0% ( $P = .7$ )	47% vs 62% ( $P = .2$ )
Retention	0% ( $P = .8$ )	77% vs 52% ( $P = .01$ )
Physical health side effects	39% ( $P = .2$ )	27% vs 48% ( $P = .04$ )
Mental health side effects	0% ( $P = .5$ )	19% vs 52% ( $P < .001$ )

**TABLE 3** Response to perampanel—comparison of studies

are detailed in Table 2. Data for both ID groups are also pooled in this table. Figure 1 shows forest plots summarizing differences in outcomes between ID sub-groups in both studies and for pooled data from both studies. Pooled estimates are shown based on a fixed effects model but consistent results were found using a random effects model. The level of heterogeneity across studies is quantified using the  $I^2$  statistic in Table 3.

Recorded rates of seizure reduction were lower in the UK population with just under half of UK participants (47%) appearing to benefit from a reduction in seizures by 12 months, whilst in the Netherland population this was 62%. Seizure reduction was a descriptive measure, defined by a clinically documented decrease in seizure frequency. These differences were not however statistically significant ( $P = .2$ ). There was also no statistical significance when ID groups were compared within studies or when the data were pooled (RR of response for moderate to profound versus mild ID: 1.09, 95% CI 0.77-1.54).

Despite similarities in seizure reduction, there is significant variation in retention rates, with only half (52%) of Dutch patients remaining on PMP after 12 months, but over three quarters (77%) of the UK patients still taking PMP ( $P = .01$ ). However, there was no evidence of study heterogeneity when comparing retention across ID groups ( $I^2 = 0$ ;  $P = .8$ ). Both studies indicate that those with severe/profound ID have higher retention rates (RR of response for moderate to profound versus mild ID: 1.37, 95% CI 1.08-1.73).

Side effects were reported more prominently in the Dutch patient cohort, for both mental health/behavioural (52% Dutch, 19% UK;  $P < .001$ ) and physical health side effects (48% Dutch, 27% UK;  $P = .04$ ). There was no evidence of variation between mild and moderate/profound ID groups in the level of physical or mental health side effects in each study and when study cohorts are combined (Figure 1).

## 5 | CONCLUSIONS

The decline in seizure frequency for ID patients who have been prescribed PMP reported in this paper is similar to data reported for non-ID patients in three (phase III) drug trials.<sup>6,7,9</sup> This adds to the evidence suggesting that PMP has a similar impact on seizure reduction for people with adult pharmacoresistant epilepsy with or without ID.

Our data indicate that despite the comparable reports of seizure reduction in our UK and Dutch ID patient cohorts, retention rates

are statistically different. Discontinuation has been linked to side effects for the Dutch cohort previously,<sup>11</sup> and the data reported in this paper highlight the significantly higher number of reported side effects (physical and mental) when the Dutch cohort is compared with those from the UK. Fewer reported side effects in the UK cohort may therefore have some impact on the higher retention rates for PMP. This could be due to slower titration patterns in the UK for people with ID.<sup>10,16</sup>

Pooling data from the two studies and comparing ID groups has indicated that people with severe/profound ID may have higher retention rates than those with mild ID. This trend is apparent despite similarities in reported-side effects across ID groups in both settings, indicating that in this instance there is no evidence to suggest side effects are of such significance to impact retention in this sub-group.

There are limitations with this study. Data collected from medical records at each site were dependent on the quality and accuracy of clinical data recorded and available to be captured. Each study involved people treated by different clinicians and in the UK at a number of different institutions. Clustering by clinician/institution was not considered. Differences in side effects such as mental health side effects may for example relate to how often each individual was seen at each institution and how much depth of information is sought and also recorded by Clinicians.

Diagnosis in both settings was completed by Dutch and UK specialists following the ILAE criteria. However, diagnosing seizures in people with ID is challenging and likely to have higher levels of error than in general population. Particularly, there may have been discrepancies in diagnosing sub-types which may explain the large differences reported regarding general versus focal seizures, such as complex partial seizures with secondary generalization as versus idiopathic generalized epilepsy in people with ID. Further, many people with ID have multiple seizure types not to mention behavioural or neuromuscular issues which can further confound the picture. Thus, it was felt that we look to capture "epilepsy" or "seizures" principally.

The UK data are also confined to individuals who consented to access to their medical records to be included in a research database. Dutch patients may choose to consent to use of their data when becoming a patient with the centre. Confounders include possibility of slower titration and that in the UK people with ID are community based whilst majority of the Dutch ID sample are supported in an institutional model. Our analyses of demographic and clinical characteristics suggested the presence of considerable heterogeneity

between studies. There is no accepted statistical approach to meta-analysis of only two studies in the presence of heterogeneity.<sup>14</sup>

The study however illustrates how taking a European perspective and sharing anonymous data across centres offers the possibility for strengthening evidence around the prescribing of AEDs in complex and difficult to research populations, such as those with ID and epilepsy. Comparing the Dutch and UK data by combining data sets for deeper analysis furthers discussion around positioning the use of PMP with ID populations.

### CONFLICTS OF INTEREST

RS and BM have received institutional and research support and personal fees from UCB, Eisai, Special Products and Desitin outside the submitted work. JA and WH have been supported by an independent investigator grant part funded by Eisai. FS, IT, JvO, JS, MM and SH have no conflict of interest to report.

### DATA AVAILABILITY STATEMENT

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

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### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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