# TITLE: Worth the paper they’re printed on? Findings from an independent evaluation of how understandable patient information leaflets for antiseizure medications are.

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# ABSTRACT

**Introduction:** The Patient Information Leaflet (PIL) is an authoritative document that all people with epilepsy (PWE) in the European Union receive when prescribed anti-seizure medication (ASM). We undertook the first independent, comprehensive assessment to determine how understandable they are. Regulators state that when patients are asked comprehension questions about them, ≥80% should answer correctly. Also recommended PILs have a maximum reading requirement of US Grade 8.

**Methods:**

***Study 1:*** Obtained 140 current ASM PILs written in English. ‘Readability’ assessed using 4 tests, with and without adjustment for influence of familiar, polysyllabic words. 179 online materials on epilepsy also assessed.

***Study 2:***Two PILs from Study 1 randomly selected (Pregabalin Focus; Inovelon) and shown to 35 people from UK epilepsy population. Their comprehension was assessed.

***Study 3:***To understand whether student population provides accessible alternative population for future examination of ASM PILs, Study 3 was completed. Used same methods as Study 2 but participants were 262 UK university students.

**Results:**

***Study 1:*** No PIL had a reading level of Grade 8. Median was 11. Adjusting for context, the PILs were still at Grade 10.5. PILs for branded ASMs were most readable. PILs were no more readable than (unregulated) online materials.

***Study 2:*** Users struggled to comprehend the PILs key messages. The 8 questions asked about pregabalin were typically answered correctly by 54%. For Inovelon it was 62%.

***Study 3:*** Most student participants comprehend the PILs key messages. The questions about Inovelon were answered correctly by 90%; for pregabalin it was 86%.

**Significance:** This is the first independent and comprehensive examination of ASM PILs. Found PILs being used fail to meet recommendations and regulatory requirements and risk not being understandable to substantial proportion of users. In finding that people from epilepsy population differ markedly in comprehension of PILs compared to students, study highlights importance of completing user testing with the target population.

**KEYWORDS:** Anticonvulsants; Epilepsy; Comprehension; Pregabalin; rufinamide; Epilepsy; Pamphlets; Self-Management.

**KEY POINTS:**

1. The PIL – as the only document all PWE in the European Union prescribed ASMs routinely receive – could be key to self-management.
2. No independent evidence is available on the understandability of ASM PILs.
3. We found none of the 140 PILs for ASMs used in the UK met the recommended maximum for reading age.
4. When PWE were shown 2 of the PILs they struggled to comprehend their key messages on how to safely and effectively use the related ASM.
5. Only 2/16 comprehension questions asked of PWE were answered by a sufficient proportion to satisfy the threshold regulators recommend.

## INTRODUCTION:

People with epilepsy (PWE) and their significant others assume substantial responsibility for the management of epilepsy. To make informed decisions, they need understandable information.1 The Patient Information Leaflet (PIL) – which has accompanied medicines in the European Union (EU) since 1999 – forms an authoritative document all people receive about their anti-seizure medication (ASM).2 How understandable are they?

Most economically developed nations include a significant minority of people with low literacy levels. In England, 15% of adults have a literacy level at or below that of an 11-year-old.3 A further 28% have a reading age of a 12-14 year old.3 When information exceeds someone’s literacy level there is the potential for misunderstandings. It has been recommended written materials have a maximum required reading age of ~13-14 years (United States [US] Grade 8).4

We systematically searched for studies examining ASM PILs. Five 5-9 were identified (Supplementary File 1). Only one examined European PILs. Conducted by Wong,9 it focused on the PILs for 12 branded ASMs written in English. The length of the sentences used and the complexity of the words within them was quantified. Based on this assessment and comparison to reference data, Wong concluded the PILs should be relatively understandable to United Kingdom (UK) adults, with the text being classified as representing ‘Plain English’. However, published in 1998 and focusing on only branded ASMs,9 Wong’s study tells us little about the understandability of current PILs.

Within the EU, the European Medicines Agency (EMA), and national competent authorities, approve PILs before use.10 They state PILs should be designed and worded so a maximum number of people can understand them.11 Since 2005, manufacturers have also legally been required to engage with users to develop their PILs.

A debate is occurring as to whether the EMA’s processes are sufficient.12, 13 It would be appropriate for the epilepsy community to contribute. In England alone in the 12 months from 1/12/2020 there were >30M ASM prescriptions.14

### What evidence is needed on ASM PILs?

Different methods are available to determine how understandable ASM PILs are.15

#### Readability

One way to gauge how understandable ASM PILs are is by using automated readability tests. These use different text characteristics to estimate ‘reading ease’. Word length is used as a proxy for semantic difficulty, whilst sentence length indicates syntactic complexity. A numeric value is assigned to the text to indicate its ‘readability’.16

A standard application of readability tests to ASM PILs would provide evidence on their ease of use in a common format and allow comparison to PILs for other medications.17 It would be helpful though to also apply them whilst adjusting for context. This is because for many readability tests, the more polysyllabic words present within a document the higher the judged required reading age. The challenge is many polysyllabic words within a PIL (e.g., convulsion, levetiracetam) may be uniquely familiar to the target audience and so be poor predictors of readability. Without adjusting for this, a test might artificially inflate required reading age.18

Regulators have made a PIL template available to manufacturers and stipulate standard headings. Some commentators contend this inadvertently reduces the readability of PILs (e.g.19, 20). In assessing ASM PILs it would thus be insightful to compare their readability to materials on epilepsy written in English for PWE, whose presentation is less regulated. Online materials meet these criteria.

#### Literal comprehension

A second way to assess the PILs would be by determining their comprehensibility. Readability does not guarantee comprehension since factors beyond text characteristics affect it (e.g., prior knowledge, interest, how information is presented).21

No published evidence on the comprehensibility of ASM PILs is available. It could be obtained by completing so-called ‘user testing’. ‘User-testing’ (as per the Australian-Sless method 22) involves a PIL being given to ~20 individuals from the target population. They are asked questions to assess the PIL’s ability to ensure people can find and understand information pertinent to the medicine’s safe and effective use. Regulators cite it as a way manufacturers can demonstrate their PIL is ready for use; stating a PIL should be iteratively refined and retested until each question is answered correctly by ≥80% of users.11, 23

‘User testing’ is resource intensive since there is a need to recruit people from the target population. When they have a stigmatising condition, this can be challenging. Funding for researchers undertaking user-testing is also not forthcoming. To position the epilepsy community to independently check ASM PILs in the future it would be helpful to understand whether PILs could be tested with populations more accessible to academic investigators. One they can recruit from in large numbers is the student population. To be a suitable alternative for testing, the student population’s pattern of comprehension results would need to be broadly indicative of those of the epilepsy population.

#### Objectives of current study

Given the information gaps identified, we conducted a series of studies that sought to:

1. describe the readability of current PILs for ASMs prescribed in the UK (study 1);
2. explore factors associated with their readability (study 1);
3. compare the readability of PILs to online epilepsy materials (study 1);
4. complete ‘user testing’ of a sample of ASM PILs to understand their comprehensibility to persons from the epilepsy population (study 2);
5. complete ‘user testing’ of the same ASM PILs but with a larger sample of persons from the student population (study 3).

**METHODS & MATERIALS**

**Study 1 -Readability of PILs**

**Design**

Cross-sectional assessment of PILs for ASMs.

**Materials**

***Patient Information Leaflets***

In the UK, 27 active ingredients are approved for epilepsy 24 (Table 1). The PILs for the 148 medications containing them were obtained on 6/10/2020 from the Electronic Medicines Compendium; 140 (94.6%) were in a format that permitted testing. Supplementary File 2 lists them.

***Online materials to compare PILs to***

A representative sample of 179 online epilepsy materials encountered by PWE was compiled (median word count of 1179, interquartile range [IQR] 695 to 1916). Supplementary File 3 lists them and their identification. In brief, 5 internet searches were completed on 6/10/2020 using search ‘terms’ PWE use (i.e., “epilepsy symptoms”, “what is epilepsy”, “epilepsy seizures”, “epilepsy uk” and “epilepsy medication”). Two reviewers independently screened the first 100 results from each search to identify eligible materials.

***Preparation of materials for testing***

Individual Microsoft Word versions of the PILs and online materials were created. No pictures, symbols, copyright notices, citations, advertisements or internet addresses were included.

In line with standard practice,25 the PIL versions included text from five of the six sections that form a PIL in the UK and EU – ‘1. What X is and what it is used for’, ‘2. What you need to know before you<take> <use> X’, ‘3. How to<take> <use> X’, ‘4. Possible side effects’ and ‘5. How to store X’. We excluded section ‘6. Contents of the pack and other information’ since patients do not rate the information contained within it as particularly important.13, 25

The Word versions of the online materials included only text from the ‘landing’ page.

**Tests**

The following established tests which consider different text characteristics and estimate years of US schooling required were used: Simple Measure of Gobbledygook (SMOG),26 Flesch–Kincaid (F-K) 27 and FORCAST.28 As per previous studies,16, 29 a composite score for each document was formed based on its median score on the tests. It can be converted to UK reading age by adding 5.

To provide a measure of readability on a continuous scale, the Flesch Reading Ease (FRE)30 test was also used. Ranging from 0 to 100, higher scores indicate greater readability. Supplementary File 4 details the formulae of each test.

Tests were completed using Readability Studio Professional Edition (V.2019). They were first run in the standard way and then whilst adjusting for context (see below).

***Adjustments for context***

A list of words was compiled for exclusion from consideration by the testing software. It comprised the n=59 words that create the generic and branded names of the ASMs, n=78 key epilepsy terms, and n=1464 adverse event terms. Supplementary File 5 details them and the rationale. The testing software was also instructed to exclude proper nouns and to treat all numerals as monosyllabic words.

**Analysis**

As the readability data was not normally distributed (Shapiro Wilk, Ps<0.01), analyses were completed using non-parametric tests (Mann-Whitney, Wilcoxon Signed Rank Test Spearman’s rank test). Central tendency is described according to the median (Mdn) and IQR. The proportion of PILs satisfying the recommended reading Grade 8 level is described.

Factors explored for their association with PIL readability were: time since the ASMs focused had been authorised for us and time since the PIL examined had been revised;31 whether the ASM was branded or generic32; and extent to which the ASM was prescribed, with PILs for the three most commonly prescribed ASMs in England (lamotrigine, levetiracetam, valproate)33 being compared to the others. These analyses were completed using data from when the readability tests were adjusted.

For the main analyses, alpha was set at 0.05. When exploring factors associated with readability, alpha was Bonferroni adjusted (p<0.006).

Analyses were conducted using SPSS (V.27).

**Study 2. User testing with people from the epilepsy population**

***Design***

An anonymous, cross-sectional online survey was run using Qualtrics. To minimise participant burden, we tested comprehension of 2 PILs. Order of presentation was randomised (1:1).

***Recruitment***

As is standard for ‘user testing’,11 a sample of ~n=20 users was sought, whilst recognising a need to account for potenital missing data.

Between November 2021 and February 2022, a participant advertisement was distributed using different social media platforms by UK epilepsy user groups (see Acknowledgements). Table 2 shows the eligibility criteria and approvals.

Approval was provided by the University of Liverpool’s Health and Life Sciences Research Ethics Committee (Ref: 7766). All participants provided informed consent.

***Materials***

To select the 2 PILs we stratified the PILs assessed within Study 1 by their adjusted FRE score. We then randomly selected one PIL from the top quartile (namely, Inovelon film-coated tablets) and one PIL from the bottom quartile (Pregabalin Focus) (Table 3).

***Survey content***

Participants were asked brief questions about demographics and epilepy profile (or that of the person they knew). For each PIL, the participant was then asked 8 comprehension questions (Table 4).

PILs remained available to participants when answering the questions and no time-restrictions were applied. Participant typed their answers to the questions within free-text boxes.

In developing the comprehension questions, regulatory guidance 11, 34 was followed. Most were framed as scenarios, asking participants in an open-ended way what the correct course of action was. Some requested the person to imagine finding themselves in a certain situation, others asked them to imagine someone they knew found themselves in the situation. This approach is consistent with guidance 11 and has been used before (e.g.,35). It also permitted the same set of questions to be used with all participants regardless of their characteristics (e.g., questions regarding female birth control and breastfeeding could be asked of all). Questions were phrased differently from the relevant text of the PILs, and the order of the topics asked about differed from the PIL. Face-validity was confirmed by a consultant neurologist.

**Analysis**

Responses to the comprehension questions were coded as correct or incorrect by 2 independent raters based on criteria established a priori. Any discrepancies were resolved through discussion. Raters were trained undergraduate psychology students (NC, SH). To understand interrater reliability, percentage agreement and the prevalence-adjusted bias-adjusted kappa (PABAK) were calculated.36

The primary analysis focused on participants who completed comprehension questions for both PILs. As comprehension scores were not normally distributed (Shapiro Wilk, Ps<0.01) central tendency is described according to the median and IQR. The proportion of participants providing a correct response to each question is reported, along with 95% confidence interval (CI). Questions for each PIL were ranked according to the proportion of correct responses elicited.

To understand how participants answering comprehension questions for 2 PILs (completers) compared to those completing them for only 1 PIL (non-completers), the total comprehension scores the two groups achieved on their first allocated PIL was calculated.

Analyses were conducted using SPSS (V.27), StatsDirect3 was used for CIs and PABAK determined using: <https://labplantvirol.com/kappa/online/calculator.html>.

**Study 3. User testing with student population**

***Design***

An anonymous, cross-sectional online survey similar to that used for Study 2 was employed.

***Recruitment***

A sample size calculation was completed. It was informed by Biggs et al.'s 5 estimate that 83% of children without epilepsy can potentially answer comprehension questions correctly having read a ASM PIL. This, together with a required confidence level of 95% and precision of ±5%, indicated 214 participants with complete data were required.

Between January and February 2022, participant advertisements were sent by email to students at the University of Liverpool within the schools of engineering, geography, management and health and life sciences. Table 2 shows the eligibility criteria.

Approval was provided by the University of Liverpool’s Health and Life Sciences Research Ethics Committee (Ref: 7766 Amend). All participants provided informed consent

***Materials, Survey Content and Analysis***

These were the same as for Study 2. The only difference was the comprehension scores of completers and non-completers were formally compared (Mann–Whitney, alpha 0.05.).

**RESULTS:**

**Study 1 -Readability of PILs**

**Characteristics of PILS**

Of the 140 PILs, 79 (56.4%) were for generic ASMs. The median authorisation date for the ASMs focused on by the PILs was 3.10.2011 (IQR 31.12.2005 to 14.12.2015); 106 (75.7%) of the ASMs had been authorised after October 2005. The median date on which the PILs examined had been last revised was 1.11.2019 (IQR 1.04.2019 to 1.03.2020).

The PILs had a median word count of 2439.5 (IQR 2116 to 2958.8), of which 17.5% of the words (IQR 15.8 to 19.4) were polysyllabic. Sentences within the PILs had a median length of 14.1 words (IQR 12.9 to 14.9).

**Readability of PILs**

*According to standard test approach*

No PIL had a reading grade score at or below Grade 8. The estimated the median required reading grade of the documents was 11.2 (IQR 10.9 to 11.5) – equivalent to a UK reading age of ~16 years (Table 1). The median FRE score of the PILs was 50 (IQR 45 to 55).

Scores on F-K, SMOG and FORCAST were all significantly correlated with one another in the expected direction (*r* range 0.629 to 0.969, all p<0.001).

*When adjusting for context*

The adjustments reduced the proportion of polysyllabic words within the PILs by a median of 3.6% to 14.3% (IQR 12.5 to 15) and led to the median reading grade requirement of the PLS reducing to 10.5 (IQR 10.2 to 10.7; z=-10.296, p<0.001). FRE score also significantly improved to 60 (IQR 57 to 64; z= 10.282, p<0.001). Nevertheless, only one (0.7%) PIL had a reading grade at or below Grade 8.

*Factors associated with PIL readability*

Time since the ASM was authorised and time since the PIL examined had been last revised were not significantly correlated with required reading grade (*rs* 0.04 to -0.17) or FRE score (*rs* -0.05 to .06). Moreover, PILs authorised before and after October 2005 did not significantly differ.

Compared to PILs for generic ASMs, PILs for branded ASMs had a significantly lower required reading grade (Md 10.3, IQR 10.2 to 10.6 vs. Mdn= 10.6 IQR 10.3 to 10.8; U= 1689, p<0.008) and higher FRE score (Mdn 62, IQR 59 to 64 vs. Mdn= 59, IQR 57 to 63; U= 3150.500, p<0.006). PILs for branded and generic were similar in word count (U=2690; p>0.05), but branded PILs included a smaller proportion of polysyllabic words (13.5 vs 14.6%; U=1724.000; p<0.006).

The required reading grade for the PILs for the most prescribed ASM ingredients was not statistically different to that of PILs for the ASMs with another ingredient (p=0.27). They did have a slightly worse FRE score (Md 58, IQR 56 to 63) but this was not significant at the Bonferroni-corrected level (Md 60 IQR 58 to 64.5; U=1453., p=0.01).

*Comparison of the readability of PILs with online epilepsy materials*

No statistically significant differences were found to exist between PILs and online materials (all p>0.05). Their unadjusted median required reading grade was 11.1 (IQR 10.5 to 11.7), their FRE 51 (IQR 44 to 58) and 4 (2.2%) items had a reading grade at or below 8.

**Study 2. User testing with people from the epilepsy population**

**Characteristics of participants**

Thirty-five participants from the epilepsy population were recruited. Complete responses to the comprehension questions were provided by 24 (68.6%). It took them a median of 26 minutes to complete the survey (IQR 10.1 to 37.8).

Their median age was 42 (36-45), most (n=22; 91.7%) were female and most (n=21; 87.5%) took part because they had epilepsy (Table 5). In terms of education, the highest attainment for 12 (50.0%) participants was a basic school certificate (typically completed at the age of 16 in the UK), 1 (4.2%) had completed an advanced school certificate (aged 18 in the UK), 4 (16.7%) had completed a university degree and 5 (20.8%) a postgraduate degree. For 2 (8.3%) participants the education level was not clear.

**Comprehension**

***Interrater reliability***

Rater agreement was excellent (Table 4). For the Inovelon PIL, raters agreed between 88.6 and 100% of the time (PABAK 0.77 to 1). For the pregabalin PIL, raters agreed between 85.7 and 100% (PABAK 0.71 to 1).

***Participant comprehension***

*Completers vs non-completers*

The median number of correct answers that completers (5, IQR 2.5 to 6) and non-completers (5, IQR 4 to 6) achieved for their first allocated PIL was similar.

*Pregabalin*

The median proportion of participants providing correct responses to the individual questions was 54.2% (range 25.0 to 83.3%). Only one question (number 8) satisfied the regulators ≥80% threshold (Table 4). Question 3 elicited the least correct responses.

*Inovelon*

The median proportion of participants providing correct responses to the individual questions was 62.5% (range 33.3 to 83.3%). One question (number 5) satisfied the ≥80% threshold. Question 2 elicited the least correct answers.

**Study 3. User testing with student population**

**Characteristics of participants**

Two-hundred and sixty-two participants were recruited; 237 (90.5%) provided complete responses to the comprehension questions. Median age was 20 (IQR 19-22), 66.2% were female and 24 (10.1%) reported English was not their main language. Seven (3.0%) reported having an epilepsy diagnosis (Table 5). They took a median of 17.5 minutes to complete the survey (IQR 13.8 to 23.4).

**Comprehension**

***Interrater reliability***

Agreement between raters was excellent (PABAK 0.72 to 1) (Table 4).

***Participant comprehension***

*Completers vs non-completers*

The median number of correct answers that completers (7.0, IQR 6 to 8) and non-completers (7, IQR 6 to 8) gave for their first allocated PIL did not significantly differ (U= 2589.5, p>0.05).

*Pregabalin*

The median proportion providing correct responses to the individual questions was 86.5% (range 48.1 to 95.4%) (Table 4). Six had ≥80% of participants providing correct responses to them. The question eliciting the least correct responses was question 1.

*Inovelon.*

The median proportion of participants providing correct responses to the individual questions was 90.9% (range 70.9 to 97.0%). Six had ≥80% of participants providing correct responses to them. The question eliciting the least correct responses was question 7.

**DISCUSSION**

**Main findings**

Our comprehensive assessment suggests ASM PILs available in the UK will not be understood by a substantial proportion of the epilepsy population.

We assessed 140 PILs using readability tests. None had a reading age at or below the recommended Grade 8 level. Most were Grade 11 – similar to PILs for other medications.13, 17 Based on literacy level data, ~40% of the general adult population in the UK might struggle with the PILs.3 It could be worse in the epilepsy population since it is at higher risk of low literacy.37

We were cognisant that readability tests might, when applied in a standard way, not offer an accurate assessment. However, even after adjusting for this, the PILs still had too high a reading level (Grade 10.5).

Despite all the regulations, templates, and guidelines in place to support PIL development, they performed no better than online materials on epilepsy. By some measures, the later were marginally better.

 There was some evidence that PILs for branded ASMs were more readable than those for generics. However, even branded PILs were written at too high a level (Grade 10.3).

To our knowledge, this is first time a difference between branded and generic PILs in Europe has been reported. The practical relevance of the difference is unclear. It is nonetheless concerning. Generic ASMs are commonly prescribed in the UK 38 and there is momentum to use them more. Why the difference occurred is unknown. It is the case that applications for authorisation for generic and branded medications in the EU can be submitted and reviewed slightly differently.10 This might be relevant.

 Whilst readability tests are helpful, how a document performs with its intended user is the most important test. For Study 2 we recruited 34 people from the epilepsy population and presented them with 2 PILs. Only 2 of the 16 questions had sufficient people answering them correctly to meet the ≥80% threshold cited by regulators.

 The size of the sample we used for Study 3 was in line with that recommended. Nevertheless, it does lack precision. Thus, it is helpful to consider the confidence intervals for the estimates. Even if the upper bounds of the intervals are used, half of the comprehension questions still fail to satisfy the ≥80% threshold.

The consequences of a person failing to understand a PIL will be context dependent. PILs are also only one way that patients can obtain information about their medications. Deficiencies in the understandability of PILs could, for instance, be mitigated by any counsel the patient receives from their care provider/s. Nevertheless, it is concerning that the questions eliciting the most incorrect responses in Study 2 related to safety warnings released for the two ASMs – namely, potential consequences of taking Inovelon if one has a pre-existing heart condition 39 and the risks of taking pregabalin with oxycodone.40

Only a small number of studies 17 have assessed how well users of other medications *comprehend* materials written for them about their medication and variability in the methods used prevents direct comparisons. Nevertheless, the studies do indicate ASM PILs are not unique in their failure to ensure patients consistently comprehend core messages (e.g.,41-43). Another important finding from some of these other studies is that they showed how PILs can be successfully modified, and patient comprehension improved.

**Findings in relation to regulations**

Criticisms of PILs are not new.44 However, most studies from Europe have focused on PILs developed before the 2005 requirement of manufactures to demonstrate engagement with users. 13 Most of the PILs we examined had been authorised after 2005. Why then did they perform so poorly?

Were the 2 PILs we considered outliers? Unlikely. We randomly selected them and included one from the quartile with the best readability score from Study 1.

A second possibility is our participants were unrepresentative. Our participants did report poor seizure control. However, they had characteristics that should have made comprehending the PILs easier. They were more educated than would be expected (37.5 % were working towards/had achieved a university degree compared to 27.1% in England45) and ~12% reported some familiarity with one or more of the ASMs focused on by the PILs.

Thirdly, might the way we conducted the user testing differ from the approach used by manufacturers? This is hard to know. The evidence manufacturers submit to regulators is not publicly available.

If we assume manufacturers all use the Australian-Sless method, then it is true that some differences existed in how we conducted the user testing. However, these should not account for the PILs performing so poorly.

One difference was (partly because of COVID-19) that we assessed comprehension via a survey, rather than by face-to-face interview. The approach has been used before.35, 46 Might it though have meant people were less likely to be scored as having given a correct response (e.g., answers could not be explored)? Our findings suggest not since the answers people typed were clear enough for two raters to consistently agree on their correctness.

What about that people viewed the PILs electronically rather than as paper documents? Could this have made the PILs less easy to comprehend? Possibly. However, PILs are used by people in this form and doing so can allow them to overcome complaints about paper PILs (e.g., zooming in to increase text size, using ‘word’ search function).47

Finally, the assessment process we used with users was abbreviated. We asked users 8 questions regarding each PIL. The Australian-Sless method involves users being asked more (~15). Half of these typically ask the person to show where specific information in the PIL is; the other half asses the person’s comprehension of that information. Regulators state ≥80% of participants should be able to both find information and answer related comprehension questions. To minimise participant burden, we only assessed participants’ comprehension (i.e., we did not ask participants to show where the information was, nor award marks for this). This difference should not explain why PILs performed so poorly in our study since we simply described the proportion of participants giving correct answers to the different questions and the number satisfying or exceeding the 80% threshold cited by regulators.

**Implications**

Our findings have relevance for both the UK and the EU. All the PILs examined had been approved whilst the UK was an EU member. Moreover, the processes the UK uses now it has left the EU remain similar.48

One interpretation of our findings is more regulation and guidance on PIL development is required. We contend there is a need to first determine how well current regulations on involving users are being adhered to by manufacturers and enforced by regulators. User involvement should be meaningful, not a ‘tick-box’ exercise. Regulators could clarify the situation by including within the Public Assessment Reports they publish 49 detailed evidence on what user engagement manufacturers did. In the meantime, the identified limitations of PILs highlight the importance of pharmacists and other care providers providing comprehensive medication counselling when dispensing any new ASM.

It would be helpful if the epilepsy community could periodically complete independent evaluations of ASMs. Funding for such work is limited. We explored the utility of completing user testing with the student population. Whilst straightforward to recruit and assess, their comprehension scores were not indicative of those of the epilepsy population. At least 80% of the student sample answered 12 of the 16 questions correctly. Moreover, the questions they struggled with most differed. Alternative ways to support independent assessments of ASM PILs warrant consideration.

**Strengths and limitations**

Our identification of the identified PILs was systematic, the assessment comprehensive and reporting transparent. The online materials we compared the PILs to were systematically identified and representative.50, 51 As shown by our systematic literature search, we are presenting the first published evidence on user testing of ASM PILs with the epilepsy population.

A potential weakness of our studies is the PILs are reflective of those available at one point in time. Some may have since been updated and understandability improved. This seems unlikely since no substantive changes to how PILs are approved have been introduced. Also, we did not find time since authorisation or revision to be related to readability in Study 1.

**CONCLUSION**

PILs are a mandatory document all people prescribed ASMs receive. Our independent and comprehensive examination of them suggests those being used in the UK will not be understandable to a sizeable proportion of the epilepsy population.

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**AUTHOR CONTRIBUTION:**

**Adam J. Noble** (Senior Lecturer in Health Services Research) was chief investigator, conceived of the study, led its design, supervised and coordinated the study, the analysis and interpretation of the data and wrote the final report.

**Niamh Coleman** and **Sarah Haddad** (Research Assistants) contributed to the running of, and recruitment for Studies 2 and 3 and scoring of comprehension responses. They also assisted with the systematic review of the literature.

**Anthony G. Marson** (Professor of Neurology and Consultant Neurologist) contributed to the design of Study 2 and 3, the interpretation of results and reviewed the final report.

**CONFLICT OF INTEREST/ ETHICAL PUBLICATION STATEMENT:**

None of the authors has any conﬂict of interest to disclose. 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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**TABLES**

**Table 1** The Patient Information Leaflets for anti-seizure medications that were tested and their readability score by their ‘active ingredient’

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Active ingredient** | **Number****of PILs that could be analysed** | **Flesch Kincaid grade level** | **FORCAST grade level** | **SMOG grade level** | **Median grade level** | **Flesch Reading Ease** |
| ***Application*** | ***Application*** | ***Application*** | ***Application*** | ***Application*** |
| Standard  | Adjusted for context | Standard  | Adjusted for context | Standard  | Adjusted for context | Standard  | Adjusted for context | Standard  | Adjusted for context |
| *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* | *Median**(IQR)* |
| Acetazolamide | 1 | 9.5- | 7.9- | 10.7- | 10.3- | 9.5- | 7.9- | 10.7- | 10.3- | 53.0- | 63.0- |
| Brivaracetam | 2 | 7.8(7.7 to .) | 6.5(6.4 to .) | 10.4(10.3 to .) | 9.8 (9.8 to .) | 7.8(7.7 to .) | 6.5(6.4 to .) | 10.4(10.3 to .) | 9.8 (9.8 to .) | 62.5(61.0 to .) | 70.5 (70.0 to .) |
| Carbamazepine | 5 | 7.8(7.7, .) | 6.5(6.4 to .) | 10.3 (10.3 to .) | 9.8(9.8 to .) | 7.8(7.7, .) | 6.5(6.4 to .) | 10.3 (10.3 to .) | 9.8(9.8 to .) | 62.5(61.0 to .) | 70.5(70.0 to .) |
| Cannabidiol  | 1 | 9.4- | 8.0- | 10.4- | 10.2- | 9.4- | 8.0- | 10.4- | 10.2- | 56.0- | 65.0- |
| Clobazam | 9 | 8.1(8.1 to 8.8) | 7.1(7.0 to 7.5) | 11.0(10.9 to 11.1) | 10.4(10.4 to10.6) | 8.1(8.1 to 8.8) | 7.1(7.0 to 7.5) | 11.0(10.9 to 11.1) | 10.4(10.4 to10.6) | 57.0(54.0 to 58.0) | 63.0(61.5 to 64.0) |
| Clonazepam | 3 | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6 to .) | 10.1(10.1 to .) | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6 to .) | 10.1(10.1 to .) | 62.0(61.0 to .) | 68.0(67.0 to .) |
| Eslicarbazepine acetate | 3 | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6 to .) | 10.1(10.1 to .) | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6 to .) | 10.1(10.1 to .) | 62.0(61.0 to .) | 68.0(67.0 to .) |
| Ethosuximide | 2 | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6, to .) | 10.1(10.1, to .) | 7.6(7.6 to 7.6) | 6.6(6.6 to .) | 10.6(10.6, to .) | 10.1(10.1, to .) | 62.0(61.0 to .) | 68.0(67.0 to .) |
| Gabapentin | 16 | 10.1(10.1 to 10.5) | 8.4(8.4 to 8.6) | 11.3(11.2 to 11.4) | 10.7(10.6 to 10.7) | 10.1(10.1 to 10.5) | 8.4(8.4 to 8.6) | 11.3(11.2 to 11.4) | 10.7(10.6 to 10.7) | 48.0(46.0 to 49.0) | 58.0(57.3 to 59.0) |
| Lacosamide | 2 | 10.1(10.1 to 10.5) | 8.4(8.4 to 8.6) | 11.3(11.2 to 11.4) | 10.7(10.6 to 10.7) | 10.1(10.1 to 10.5) | 8.4(8.4 to 8.6) | 11.3(11.2 to 11.4) | 10.7(10.6 to 10.7) | 48.0(46.0 to 49.0) | 58.0(57.2 to 59.0) |
| Lamotrigine | 6 | 10.3(10.0 to 10.4) | 8.3(8.2 to 8.3) | 11.1(10.9 to 11.1) | 10.3(10.3 to 10.4) | 10.3(10.0 to 10.4) | 8.3(8.2 to 8.3) | 11.1(10.9 to 11.1) | 10.3(10.3 to 10.4) | 49.0(48.7 to 50.2) | 61.0 (60.7 to 61.0) |
| Levetiracetam | 21 | 11.1(10.8 to 11.5) | 8.8(8.7 to 8.9) | 11.5(11.3 to 11.5) | 10.6(10.6 to 10.8) | 11.1(10.8 to 11.5) | 8.8(8.7 to 8.9) | 11.5(11.3 to 11.5) | 10.6(10.6 to 10.8) | 41.0(38.5 to 43.5) | 56.0(55.0 to 57.0) |
| Oxcarbazepine | 3 | 10.2(10.0 to .) | 8.7(8.3 to .) | 11.2(11.1 to .) | 10.5(10.5 to .) | 10.2(10.0 to .) | 8.7(8.3 to .) | 11.2(11.1 to .) | 10.5(10.5 to .) | 49.0(45.0 to .) | 58.0(56.0 to .) |
| Perampanel | 2 | 9.2(9.2 to 9.2) | 7.7 (7.7 to .) | 10.8(10.8 to .) | 10.3(10.3 to .) | 9.2(9.2 to 9.2) | 7.7 (7.7 to .) | 10.8(10.8 to .) | 10.3(10.3 to .) | 55.0(55.0 to 55.0) | 63.5(63.0 to .) |
| Phenobarbital | 3 | 11.2(9.9 to .) | 9.2(8.7 to .) | 11.8(11.6 to .) | 11.2(11.2 to .) | 11.2(9.9 to .) | 9.2(8.7 to .) | 11.8(11.6 to .) | 11.2(11.2 to .) | 39.0(39.0 to .) | 52.0(49.0 to .) |
| Phenytoin | 4 | 11.4(11.1 to 11.8) | 9.7(9.5 to 10.2) | 11.5(11.3 to 11.6) | 10.9(10.7 to 11.0) | 11.4(11.1 to 11.8) | 9.7(9.5 to 10.2) | 11.5(11.3 to 11.6) | 10.9(10.7 to 11.0) | 41.5(40.2 to 42.7) | 51.5(48.7 to 52.7) |
| Piracetam | 3 | 7.5(7.5 to .) | 6.2(6.2 to .) | 10.8(10.8 to .) | 10.1(10.1 to 10.1) | 7.5(7.5 to .) | 6.2(6.2 to .) | 10.8(10.8 to .) | 10.1(10.1 to 10.1) | 61.0(57.0 to .) | 69.0(67.0 to .) |
| Pregabalin | 19 | 10.1(9.8 to 10.3) | 7.9(7.8 to 8.1) | 11.6(11.5 to 11.7) | 10.8(10.7 to 10.8) | 10.1(9.8 to 10.3) | 7.9(7.8 to 8.1) | 11.6(11.5 to 11.7) | 10.8(10.7 to 10.8) | 46.0(45.0 to 49.0) | 59.0(58.0 to 60.0) |
| Primidone | 1 | 11.2- | 10.1- | 11.6- | 11.1- | 11.2- | 10.1- | 11.6- | 11.1- | 39.0- | 45.0- |
| Rufinamide | 2 | 8.6(8.6 to8.6) | 7.3(7.3 to.) | 10.6(10.6 to 10.6) | 10.1(10.1 to 10.1) | 8.6(8.6 to8.6) | 7.3(7.3 to.) | 10.6(10.6 to 10.6) | 10.1(10.1 to 10.1) | 59.0(59.0 to59.0) | 66.0(66.0 to 66.0) |
| Sodium valproate +/- Valproic acid | 11 | 9.3(9.1 to 9.6) | 7.5(7.4 to 7.7) | 11.1(10.9 to 11.3) | 10.3(10.3 to 10.4) | 9.3(9.1 to 9.6) | 7.5(7.4 to 7.7) | 11.1(10.9 to 11.3) | 10.3(10.3 to 10.4) | 53.0(52.0 to 55.0) | 64.0(63.0 to64.0) |
| Stiripentol | 2 | 9.2(9.1 to .) | 7.8(7.7 to .) | 10.7(10.7 to .) | 10.2(10.2 to .) | 9.2(9.1 to .) | 7.8(7.7 to .) | 10.7(10.7 to .) | 10.2(10.2 to .) | 53.0(52.0 to .) | 61.0(60.0 to .) |
| Tiagabine | 0 | - | - | - | - | - | - | - | - | - | - |
| Topiramate | 10 | 8.8(8.6 to 8.9) | 7.0(6.9 to 7.2) | 11.2(11.1 to 11.4) | 10.6(10.5 to 10.7) | 8.8(8.6 to 8.9) | 7.0(6.9 to 7.2) | 11.2(11.1 to 11.4) | 10.6(10.5 to 10.7) | 54.0(53.0 to 54.2) | 64.0(62.7 to 65.0) |
| Valproic acid | 1 | 9.5- | 8.1- | 11.1- | 10.5- | 9.5- | 8.1- | 11.1- | 10.5- | 52.0- | 61.0- |
| Vigabatrin | 3 | 8.5(8.3 to .) | 7.6(7.3 to .) | 11.0(10.6 to .) | 10.7(10.2 to .) | 8.5(8.3 to .) | 7.6(7.3 to .) | 11.0(10.6 to .) | 10.7(10.2 to .) | 57.0(57.0 to .) | 62.0(62.0 to .) |
| Zonisamide | 5 | 8.8(8.5 to 9.0) | 7.1(7.0 to 7.2) | 10.5(10.5 to 10.6) | 10.0(9.9 to 10.0) | 8.8(8.5 to 9.0) | 7.1(7.0 to 7.2) | 10.5(10.5 to 10.6) | 10.0(9.9 to 10.0) | 57.0(55.5 to 58.5) | 67.0(66.5 to 67.0) |
| **Total** | **140** | 9.9(8.9 to 10.5) | 8.0(7.4 to 8.7) | 11.3(10.9 t0 11.5) | 10.6(10.3 to 10.7) | 9.9(8.9 to 10.5) | 8.0(7.4 to 8.7) | 11.3(10.9 t0 11.5) | 10.6(10.3 to 10.7) | 50.0(45.0 to 55.0) | 60.0(57.0 to 64.0) |

*Notes:* FRE= Flesch Reading Ease score (0-100, higher scores equate with easier to read); FK= Flesch Kincaid reading grade score; FORCAST= FORCAST reading grade score; IQR, interquartile range; SMOG= SMOG reading grade score; Median grade score calculated on basis of FK, FORCAST and SMOG.

**Table 2.** Participant inclusion and exclusion criteria

|  |  |
| --- | --- |
| **Study 2:**  | **Study 3** |
| ***Epilepsy population*** | ***Student population*** |
| Aged ≥16 years (no upper limit) | Aged ≥16 years (no upper limit) |
| Lives in the UK | Lives in the UK |
| Able to provide informed consent  | Able to provide informed consent  |
| Able to independently read and write in English | Able to independently read and write in English |
| Self-report a clinical diagnosis of epilepsy (any syndrome or seizure type) OR be close family member or friend (significant other) to someone with epilepsy |  |
| Ineligible:► Severe current psychiatric disorders(e.g., acute psychosis)► Terminal medical illness | Ineligible► Severe current psychiatric disorders(e.g., acute psychosis► Terminal medical illness |
|  |

**Table 3.** Details of Patient Information Leaflets (PIL) selected for ‘user testing’ (Studies 2 and 3)

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **PIL 1**  | **PIL 2** |
| ***Pregabalin Focus 20 mg/ml oral solution*** | **Inovelon 100, 200, 400 mg film-coated tablets** |
| *Active ingredient:* | Pregabalin | Rufinamide |
| *Branded/generic:* | Generic | Branded |
| *Word count:* | 25487 | 1825 |
| *Flesch Reading Ease score (context adjusted):* | 56; bottom quartile | 66; top quartile |
| *Median Reading Grade Score (context adjusted):* | 11 | 10 |
| *Authorisation holder:* | Focus Pharmaceuticals Ltd. | Eisai GmbH |
| *Version date:* | February 2019 | May 2020 |

**Table 4.** Questions asked of participants about the different ASM leaflets to assess comprehension and the scores of the sample

|  |  |  |
| --- | --- | --- |
| **Patient Information Leaflet**  | **Epilepsy sample (n=24)** | **Student sample (n=237)** |
|  |  | ***Interrater reliability\**** |  |  | ***Interrater reliability\**** |
| *Correct, %* *(%, 95% CI)* | *Rank* | *PABAK* *(BI; PI)* | *Agreement* | *Correct, %**(95% CI)* | *Rank* | *PABAK* *(BI; PI)* | *Agreement* |
| ***Pregabalin Focus 20 mg/ml oral solution*** |  |  |  |  |  |  |  |  |
| 1 | Imagine you are already taking one anti-seizure medication. It is not working well. Your doctor therefore also prescribes you pregabalin. Should you stop the other anti-seizure medication? Please explain your answer. | 66.7(46.3 to 87.0) | 4 | 0.71(BI: -0.08; PI: 0) | 85.7 | 48.1%(41.7 to 54.5) | 8 | 0.90(BI: 0; PI; 0.04) | 95.0 |
| 2 | Imagine you have a family member who is taking pregabalin. They are thinking about taking the oral contraceptive pill. Explain if they can do this? | 58.3(37.1 to 79.6) | 5 | 0.94(BI: 0.03; PI: -0.06) | 97.1 | 78.1(72.8 to 83.4) | 7 | 0.95(BI: 0.02; PI: -0.55) | 97.5 |
| 3 | Imagine that as well as taking pregabalin you were also taking oxycodone for pain. Explain what may happen if you took these two medicines at the same time. | 25.0(6.3 to 43.7) | 8 | 0.94(BI: 0.02; PI: -0.51) | 97.1 | 81.0%(75.9 to 86.0) | 6 | 0.90(BI: 0.03; PI: -0.58) | 95.5 |
| 4 | Imagine that you took too much pregabalin. Explain what you should do. | 79.2(61.6 to 96.7) | 2-3 | 1(BI: 0; PI: 0.37) | 100 | 95.4%(92.7 to 98.1) | 1 | 1(BI: 0; PI: -0.90) | 100.0 |
| 5 | Imagine that you forgot to take your pregabalin when you were meant to take it. Explain what you should do. | 79.2(61.6 to 96.7) | 2-3 | 1(BI: 0; PI:0.37) | 100 | 92.8(89.5 to 96.1)) | 2 | 0.98(BI: -0.01; PI: -0.85) | 99.2 |
| 6 | Imagine your family member has been prescribed pregabalin, do they need to take food before they take it? | 50.0(28.4 to 71.6) | 6 | 1(BI: 0; PI:0: -0.31) | 100 | 82.3(77.4 to 87.2) | 5 | 0.94(BI: -0.01; PI: -0.64) | 97.5 |
| 7 | Explain how you should store the pregabalin medicine. | 41.7(20.4 to 62.9) | 7 | 0.89(BI: 0.06; PI: -0.20) | 94.3 | 90.7(86.9 to 94.4) | 4 | 0.72(BI: -0.14; PI: -0.76) | 86.0 |
| 8 | Imagine that after you start taking pregabalin you experience some mood changes or distressing thoughts. Explain what you should do. | 83.3(67.3 to 99.4) | 1 | 1(BI: 1; PI: 0.43) | 100 | 91.1(87.5 to 94.8) | 3 | 0.98(BI: 0; PI: -0.83) | 99.2 |
|  |  |
| **Inovelon 100, 200, 400 mg film-coated tablets** |  |  |  |  |  |  |  |  |
| 1 | What is the name of the medicine that Inovelon contains? | 41.7(20.4 to 62.9) | 7 | 1(BI: 0; PI: -.43) | 100 | 91.1(87.5 to 94.8) | 4 | 0.96(BI: -0.01; PI: -0.93) | 98.1 |
| 2 | Imagine you have a friend who has a family history of electrical disturbance of the heart. What might happen if they take this medication? | 33.32(12.9 to 53.7) | 8 | 0.94(BI: 0.03; PI: -.46) | 97.1 | 78.9(73.7 to 84.1) | 7 | 0.97(BI: -0.01; PI; -0.57) | 98.4 |
| 3 | Imagine that you have a family member who is breast-feeding. Explain if this person can take Inovelon. | 54.2(32.7 to 75.7) | 4-5 | 0.77(BI: 0.06; PI -0.09) | 88.6 | 95.4(92.7 to 98.1) | 3 | 0.96(BI: 0.99; PI; 0.01) | 99.6 |
| 4 | Imagine that you took too much Inovelon medicine. Explain what you should do. | 79.2(61.6 to 96.7) | 2-3 | 1(BI: 0; PI: 0.37) | 100 | 97.0(94.8 to 99.2) | 1 | 1(BI: 0; PI: -0.94) | 100.0 |
| 5 | Imagine that you forgot to take the Inovelon medicine when you were meant to take it. Explain what you should do. | 83.3(67.3 to 99.4) | 1 | 1(BI: 0; PI: 0.42) | 100 | 90.7(86.9 to 94.4) | 5 | 0.91(BI: -0.02; PI: -0.84) | 95.3 |
| 6 | Imagine your family member has been prescribed Inovelon, do they need to eat food before they take it? | 54.2(32.7 to 75.7) | 4-5 | 1(BI: 0; PI: -0.02) | 100 | 89.0(85.0 to 93.0) | 6 | 0.98(BI: -0.01; PI: -0.76) | 98.8 |
| 7 | Imagine that when you go to take the Inovelon you notice that the appearance of the tablets has changed, what should you do? | 50.0(28.4 to 71.6) | 6 | 0.94(BI: 0.03; PI: -0.17) | 97.1 | 70.9(65.1 to 76.7)) | 8 | 0.91(BI: -0.05; PI: -0.40) | 95.3 |
| 8 | Imagine that after you start taking the Inovelon medicine, you start to get a rash. Explain what you should do. | 79.2(61.6 to 96.7)) | 2-3 | 0.94(BI: -0.02; PI: 0.40) | 97.1 | 96.2(93.8 to 98.7)) | 2 | 0.96(BI: 0.01; PI: -0.94) | 98.1 |

*Notes:* BI, bias index; PI, prevalence index; \*Interrater reliability calculated using comprehension data from all participants – completers and non-completers. A PABAK value of 0.81–1.00 was considered to indicate almost perfect agreement, 0.61–0.80 substantial agreement, 0.41–0.60 moderate agreement, 0.21–0.40 fair agreement, and 0.00–0.20 slight agreement. PI can range from −1 to +1 (0 indicates equal probability), whilst BI ranges from 0 to 1 (0 indicates equal marginal proportions and so no bias).52

**Table 5.** Characteristics of participants samples for Study 2 and 3

|  |  |  |
| --- | --- | --- |
| **Factors** | **Epilepsy sample****n=24** | **Student sample****N=237** |
| **Age (years)** Median (IQR)  | 42 (36-45) | 20 (19-22) |
| **Sex** (n/ %) Male  Female Prefer not to say | 2 (8.3)22 (91.7)0 | 78 (32.9)157 (66.2)2 (0.8) |
| **Main language** English Other | 23 (95.8)1 (4.2) | 213 (89.9)24 (10.1) |
| **Relationship with epilepsy** (n/ %) I have epilepsy Significant other to someone with epilepsy  No relationship | 21 (87.5)3 (12.5)0 | 7 (3.0)44 (18.6)186 (78.4) |
| **Have you achieved, or are you currently studying for, a qualification at degree level or above?** Yes No | 9 (37.5)15 (62.5) | 234 (98.7)3 (1.3) c   |
| **How often do you have problems learning about medical conditions because of difficulty understanding written information? a**Limited health literacy (score 1-4)Adequate health literacy (score 5) | 17 (70.8)7 (29.2) | 156 (65.8)81 (34.2) |
| **Experience with any of ASMs focused on by PILs** No Yes | 21 (87.5)3 (12.5) | 231 (97.5)6 (2.5) |
| **Seizures (any type) prior 12 months b**  Median (IQR) No  Yes | 7 (2 to 10)5 (20.8)19 (79.2) | --- |

*Notes:* a Health literacy measured using validated question,53 “How often do have problems learning about medical conditions because of difficulty understanding written information?” Responses were recorded on a Likert scale from 1=all of the time, 2=most of the time, 3=some of the time, 4= a little of the time or 5=none of the time. A score of 1–4 was categorised as having limited health literacy and score of 5 as adequate health literacy; **b** Seizure frequency measured according to Thapar et al.'s 54 scale which asks “How many attacks have you had in the last 12 months?”. The patient can choose from the following ordinal categories: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more; c These n=3 participants were at the time of the survey studying at the university for a Foundation Certificate. This is not a university degree, but rather a course to prepare some international students for a subsequent undergraduate degree course.