Applying a Perceptions and Practicalities Approach to Understanding Nonadherence to Anti-Epileptic drugs (AEDs)

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Summary

Objective: Nonadherence to antiepileptic drugs (AEDs) is a common cause of poor seizure control. This study examines whether reported adherence to AEDs is related to variables identified in the NICE Medicines Adherence Guidelines as being important to adherence: perceptual factors (AED necessity beliefs and concerns), practical factors (limitations in capability and resources) and perceptions of involvement in treatment decisions.

Methods: This was a cross-sectional study of people with epilepsy receiving AEDs. Participants completed an online survey hosted by Epilepsy Society (n = 1010), or as an audit during inpatient admission (n = 118). Validated questionnaires, adapted for epilepsy, assessed reported adherence to AEDs [Medication Adherence Report Scale (MARS)], perceptions of AEDs [Beliefs about Medicines Questionnaire (BMQ)] and patient perceptions of involvement in treatment decisions [Treatment Empowerment Scale (TES)].

Results: Low adherence was related to AED beliefs (doubts about necessity: t(577) = 3.90, $p < 0.001$) and concerns: t(995) = 3.45, $p = 0.001$), reported limitations in capability and resources (t(589) = 7.78, $p < 0.001$) and to perceptions of a lack of involvement in treatment decisions (t(623) = 4.48, $p < 0.001$). In multiple logistic regression analyses, these factors significantly ($p < 0.001$) increased variance in reported adherence, above that which could be explained by age and clinical variables (seizure frequency, type, epilepsy duration, number of AEDs prescribed).

Significance: Variables identified in the NICE Medicines Adherence Guidelines as potentially important factors for adherence were found to be related to adherence to AEDs. These factors are potentially modifiable. Interventions to support optimal adherence to AEDs should be tailored to address doubts about AED necessity and concerns about harm, and to overcome practical difficulties, while engaging patients in treatment decisions

Key words: Epilepsy; Medication Adherence; Antiepileptic Drugs; Beliefs about Medicine; Treatment Decisions

Introduction

An estimated 70% of people with epilepsy could have their seizures controlled using anti-epileptic drugs (AEDs), reducing their risk of serious consequences such as sudden unexplained death, seizure and status epilepticus [1; 2]. However, approximately 21-42% of patients prescribed AEDs for epilepsy do not adhere to their prescribed treatment[3-7]. This nonadherence is associated with increases in seizure risk[8], risk of hospitalization and treatment costs[9; 10] and premature mortality [11].

A number of interventions have been designed to support people with epilepsy to self-manage their medications and/or adhere to their medication (e.g.[12; 13]; for review of RCTs see[14]). However, many interventions are not successful, and, even for those that are successful, many patients in the intervention group do not achieve high levels of adherence [14].

A comprehensive review, commissioned by the UK National Institute of Health Research (NIHR), examined the reasons *why* interventions to facilitate adherence to medication for long-term conditions have met with only limited success[15]. This drew on theories of medication adherence and explanatory studies that had identified potentially modifiable determinants of nonadherence across a range of long-term conditions, to recommend a Perceptions and Practicalities Approach (PAPA) for supporting adherence[16]. This approach proposes that nonadherence should be seen as a variable behavior rather than a trait characteristic: adherence rates vary not just between individuals but within the same person, over time and across treatments. Nonadherence may be both intentional and unintentional. In order to understand why an individual may or may not adhere to a prescribed treatment we need to consider both their motivation and ability. The PAPA suggests that adherence support will be more effective if it is tailored to meet the needs of the individual by identifying and addressing both the perceptual factors (e.g. beliefs and preferences) and practical factors (e.g. capability and resources) that influence the patient's motivation and ability to start and continue with treatment. Within this approach, barriers to adherence combine to cause nonadherence; for example, someone who experiences many practical barriers to adherence will need to be more motivated to overcome them. The approach also emphasizes the importance of patients' involvement in decisions about their medication. In previous studies, many factors have been associated with nonadherence to AEDs. For example, depression[17 18], lack of perceived social support[19], perceived stigma[20] and unemployment[21], however no studies have applied the PAPA to adherence in epilepsy. The perceptual factors influencing medication adherence are often operationalized as Horne's Necessity Concerns Framework[22]. A recent meta-analysis of 93 studies published in peer-reviewed journals and covering 23 long-term conditions in 18 countries, showed that adherence is often related to how individuals judge their personal need for treatment and to their concerns about the potential negative effects of taking it. The NICE Medicines Adherence Guidelines[23] drew on these approaches and also recommended that prescribers should involve patients in treatment decisions.

Based on theories of nonadherence[24] , we expected that reported nonadherence to AEDs would be associated with more negative beliefs about AEDs (doubts about necessity and concerns), more practical barriers (e.g. losing track of time), and to perceptions of involvement in treatment decisions. We collected data from two samples of people with epilepsy: an online survey collected by a patient charity, and an inpatient sample. We used the inpatient sample, which has an ascertained diagnosis of epilepsy and AED serum levels, to validate the self-reported adherence questionnaire in the context of online data collection.

Methods

The study comprised two cross-sectional samples of people with epilepsy, one recruited through an anonymized internet survey supported by a patient charity and the second recruited as part of an approved audit at a specialist inpatient referral centre for epilepsy at the National Hospital for Neurology and Neurosurgery. Both were exempt from ethics approval requirements: the internet survey because it was an anonymized voluntary online survey, and the inpatient data because it was an audit, as deemed and registered by the relevant independent audit group at the National Hospital for Neurology and Neurosurgery.

Recruitment

The internet sample was recruited in 2011-12 through Epilepsy Society, an epilepsy charity (www.epilepsysociety.org.uk). Participation was entirely voluntary and completely anonymous. The online survey link was placed on the website of Epilepsy Society in December 2011. Printed copies were available for people without internet access. The survey was promoted via partner organizations, radio and social media across the UK. Other organizations that promoted the survey included the International League Against Epilepsy (UK and GP branches), the Epilepsy Specialist Nurses Association, and some regional branches of the Neurological Alliance. Posters were placed in clinics at the National Hospital for Neurology and Neurosurgery in London. The survey was also promoted via Epilepsy Society's magazine, e-newsletter and social media, and via press and radio in Northern Ireland, UK.

In addition, patients admitted to the Sir William Gowers Centre, a multidisciplinary epilepsy treatment and assessment centre (a satellite of National Hospital for Neurology and Neurosurgery run in partnership with Epilepsy Society) between Jan-Oct 2013 were invited to complete the same survey in hardcopy. Patients at the Sir William Gowers Centre have planned admissions for assessment: there are no emergency, unplanned admissions. All patients included in this study were therefore already prescribed AEDs and none had treatment suspended as a result of an urgent response to another health condition. The needs of the patients were considered when distributing the survey. Patients who were admitted for less than two days and those with learning disabilities which the clinical team judged would prevent them from completing the survey were not given the questionnaire. Questionnaires were given out by staff involved in admissions (receptionist, nurse or support worker) and then returned to the reception at any time during the inpatient stay. Of patients who were admitted for two or more days, 43% completed and returned the survey. No medical staff were involved in the process and patients were informed that their responses would have no effect on their care.

Participants

In total, 1595 people with epilepsy participated through the internet survey (48 completed on paper) and 119 people with epilepsy completed the survey from the inpatient facility. We excluded 531 incomplete responses, and 55 complete responses from the internet survey: 33 who stated they lived outside the UK; 6 who completed the survey on behalf of someone else; and 16 who were not currently taking epilepsy medication. All remaining patients were UK resident, completed the questionnaire on behalf of themselves and were currently prescribed AEDs. One inpatient was readmitted and participated a second time; their second response was subsequently excluded. The final sample comprised 1127 people, of whom 118 were inpatients.

Questionnaire measures

The following measures were included in the survey.

Demographic and clinical variables

Participants were asked to report their age, how long they had had epilepsy, how often they had seizures, and what type or types of seizures they have:
seizures where I…
'am aware of what is happening (such as simple focal seizures)'
'am confused or only partly aware (such as complex focal seizures)'
'briefly lose consciousness (such as absences, tonic and atonic seizures)'
'lose consciousness and jerk or convulse (such as tonic clonic seizures)'
Participants were also asked to indicate which medications they were currently taking from a list of 24 AEDs.

BMQ-Epilepsy Specific Scales

The BMQ-Epilepsy Specific scale[25] (©R Horne) was an adapted version of the BMQ-Specific scale[26] designed to assess respondents' belief in their personal need for their AED (AED Necessity) e.g. 'I would prefer to take my epilepsy medicine rather than risk having a seizure', and their concerns about the potential adverse consequences of their AED (AED-Concerns) e.g. 'I sometimes worry that my epilepsy medicine slows me down'. The AED-Necessity scale has six items and the AED Concerns scale has ten items. Post-hoc Cronbach's α indicated that both had adequate internal reliability (AED-Necessity α=0.79; AED-Concerns α=0.80). All items were rated on a 5-point Likert-type scale (Strongly Disagree=1, Agree=2, Uncertain=3, Disagree=4 and Strongly Disagree=5). Scores were pro-rated and then mean item scores (range 1-5) were computed by dividing the scale score by the number of items in the scale. Higher scores indicate higher agreement with the construct represented by the scale.

A Necessity-Concerns Differential (NCD) was calculated by subtracting AED-Concerns scores from AED-Necessity scores. The NCD score provides a numerical indicator of how the individual judges their personal need for AED relative to their concerns about the potential negative effects of taking AEDs. NCD scores range from -4 to +4, with positive scores indicating higher ratings of AED-Necessity relative to AED-Concerns.

Finally, we divided patients into four attitudinal groups by dichotomizing participants at the scale midpoints: AED-Necessity (less than 3 as Low AED-Necessity) and AED-Concerns (greater than 3 as High AED-Concerns). Participants were then grouped into patients who were Accepting (High Necessity, Low Concerns), Indifferent (Low Necessity, Low Concerns), Sceptical (Low Necessity, High Concerns) or Ambivalent (High Necessity, High Concerns) about AED treatment[27; 28].

An additional new BMQ 6-item subscale, the AED Practical Barriers Scale (©R Horne), assessing practical barriers to adherence to AEDs, was also included. Participants were asked to rate the frequency with which they experienced six barriers to adherence e.g. 'I have difficulty swallowing my medication', on a 5-point Likert-type scale, from 1=Always, 2=Often, 3=Sometimes, 4=Rarely, and 5=Never. The scale had adequate reliability, Cronbach's $\alpha = 0.74$, but has not been previously validated.

Treatment Empowerment Scale

The Treatment Empowerment Scale (TES) is a validated measure of patients' perceptions of empowerment during medical consultations, and their perceived degree of involvement in decisions about treatment[29], e.g. 'The decision to start or stop medication is mine, not the doctor's'. Respondents were asked to rate their agreement with ten statements regarding their communication with their doctor about their epilepsy medication on a 5-point Likert scale (1=Strongly Agree, 2=Agree, 3=Unsure, 4=Disagree, 5=Strongly Disagree). These response options were adapted from the original choices to make them consistent with the other scale formats used within this study. As with the original scale, scores were reversed where appropriate, pro-rated and summed to form a total score (range 10-50). The scale had adequate reliability, Cronbach's $\alpha = 0.82$.

Medication Adherence Rating Scale

A 10-item version of the Medication Adherence Rating Scale (MARS[30]) was used to assess patients' adherence to their medication. This version of the MARS was adapted for epilepsy. Although the MARS has been previous validated[30] e.g. against prescription refill databases[31 32], electronic adherence monitors[33] and serum concentration of medication[34], our adaptation of the scale has not been validated. Patients rated ten medication-taking behaviours (e.g. 'I decide to miss out a dose') on a 5-point Likert-type scale (1=Always, 2=Often, 3=Sometimes, 4=Rarely, and 5=Never). A total adherence score, with higher scores indicating higher adherence, range 10-50, was calculated by summing responses on this scale. The scale had good internal reliability (Cronbach's $\alpha = 0.83$). As with previous studies, scores were pro-rated and then the total scale scores were dichotomized, with the third of patients scoring the lowest on self-reported adherence (≤ 44) grouped into 'low adherence' and the highest two-thirds (≥ 45) grouped into 'high adherence'[25; 28]. We described the groups as high and low rather than adherent and non-adherent as we recognized that some of the participants in the high adherent group did not report full adherence and may even have responded 'always' to one of the items.

AED blood level assessment

The inpatient sample had AED serum levels measured at the hospital's accredited Therapeutic Drug Monitoring laboratory using quality-controlled standardized procedures as part of routine clinical care. Where participants had recorded AED levels on admission or the first full day as an inpatient we assumed that AED levels would be indicative of their adherence behavior outside the hospital. Levels of AEDs were categorized as within established reference ranges (http://www.epilepsysociety.org.uk/using-tdm-service#.VEwJCRaEywQ), under or above the reference range for a given AED, or undetectable. AED serum levels have been validated as an adherence assessment in several previous studies[35-37].

Analysis

Data were analyzed using IBM SPSS Statistics 21. Independent samples t-tests were used to test for differences between high and low adherence group on perceptions of AED (AED Necessity and AED Concerns), AED Practical Barriers (e.g. difficulty swallowing or losing track of time) and perceptions of involvement in treatment decisions. Standardized effect sizes (Cohen's d) were calculated to allow the size of these differences to be compared. Correlations were used to assess relationships between perceptions of AED (AED Necessity and AED Concerns), AED Practical Barriers (e.g. difficulty swallowing or losing track of time) and perceptions of involvement in treatment decisions. Logistic regression was used to assess the relationship between clinical, demographic, perceptual and practical factors and adherence. Predictors were entered into multivariable analysis dependent on our hypotheses rather than based on which variables were significant predictors of adherence in univariable analyses. Nagelkerke's R^2 was used as an estimate of the proportion of variance in nonadherence accounted for by each predictor. Nagelkerke's R^2 is a pseudo R^2 statistic which is not equivalent to R^2 in OLS regression but which enables comparison of how well different logistic regression models fit a particular data set. Hierarchical stepwise logistic regression was used to assess the combined value of perceptual and practical barriers and treatment empowerment (added at the final step) in predicting adherence after controlling for demographic (age) and clinical variables (seizure frequency, type, epilepsy duration, number of AEDs prescribed).

Results

The results in both samples were very similar and therefore the online and inpatient samples are combined within these results. Detailed data, including individual item responses for both samples separately, are included within the supplementary information.

Clinical and Demographic Variables

Approximately three quarters of the respondents (71.4%, n = 804) were aged 25-59. Around one third of respondents (n = 396, 35.3%) reported they had been diagnosed with epilepsy for more than 20 years. Just over two-thirds of respondents reported that they had had at least one seizure in the previous year (n = 743, 68.2%). Participants could report that they experienced multiple seizure types. The most frequent type of seizure reported were those where patients lost consciousness and jerked or convulsed (e.g. tonic-clonic seizures), reported by 683 participants (60.6%). See Table 1 for full descriptive statistics.

A single medication was taken by 43.9% of participants (n = 495); two medications were taken by 31.1% (n = 351), with the remainder of participants taking more medications. The most common AED was levetiracetam, taken by 36.4% (n = 410) of participants, followed by lamotrigine taken by 32.7% (n = 369), and carbamazepine, 26.2% (n = 295). The proportions of respondents taking each particular AED are shown in Figure 1 (in the Supplementary information).

Adherence to AEDs

MARS scores were dichotomized using the scale midpoint (see Table 2) to form two groups, a group reporting high adherence (n = 764, 68.3%) and a group reporting low adherence (n = 355, 31.7%).

Sixty-three patients (52.9%) of the inpatient sample had AED blood levels taken on admission or during their first full day as an inpatient. Eight patients' blood levels indicated that at least one prescribed AED was undetectable, suggesting nonadherence. MARS scores were significantly lower for those patients who had any AED undetectable blood level than for other patients (Mann-Whitney U = 328.5, p = 0.02). Of patients who had an undetectable blood level, 50.0% (n = 4) were also categorized as low adherent on the MARS. Conversely, of the 55 patients whose drug levels indicated the presence of at least one AED, 83.6% (n = 46) were also categorized as highly adherent on the MARS. This suggests the self-report data was associated with blood level indicators of taking AEDs.

Attitudinal Analysis of Perceptions of AEDs

Participants were categorized into attitudinal groups based on whether they scored above or below the scale midpoint for the AED Necessity and AED Concerns scales (see Figure 1) into high/low concerns and high/low necessity groups. These dichotomized scores were then used to split patients into attitudinal groups. Approximately half of all participants (n = 595; 52.8%) were 'Ambivalent' about their AEDs, having a strong belief that they needed their AEDs but also high concerns about their medicines. Just over a third of participants were 'Accepting' of their AEDs (35.7%, n = 402), having low concerns and high necessity beliefs. Small proportions of patients were 'Skeptical', having both high doubts about their personal need for AEDs and high concerns (5.9%, n = 67) or 'Indifferent', reporting low concerns and low beliefs in their need for AEDs (4.9%, n = 55).

Practical Barriers to Taking AEDs

Factor analysis identified a single factor underlying the AED Practical Barriers scale. The median total score for the scale was 9.0 (IQR: 7.00-13.00) indicating that the majority of participants said that they never or rarely experienced most of the practical barriers. To aid interpretation, we counted the number of practical barriers which patients reported experiencing rarely, sometimes, often or always. The median number of practical barriers reported was 2 (IQR: 1-4). Approximately a fifth of participants (20.8%, n = 226) reported that they experienced none of the practical barriers to taking their AEDs.

Perceptions of Involvement in Treatment Decisions

Participants' scores on the treatment empowerment scale (TES; mean = 3.35, s.d.= 0.74) were around the response midpoint of 3 or Uncertain, indicating that many participants did not feel highly involved in treatment discussions and decisions.

Relationships Between Adherence to AEDs, Perceptual and Practical Barriers to Adherence and Perceptions of Involvement in Treatment Decisions

Participants in the Low Adherence group rated their personal need for AEDs lower, and their concerns about AEDs higher, than the High Adherence group. Consistent with this, their overall judgment of AEDs was more negative, as indicated by lower AED NCD scores. Participants who reported low adherence also had higher scores on the practical barriers scale (see Table 3). Comparison of the standardized effect sizes, d, indicated that the largest difference between the high and low adherence groups was on the practical barriers scale.

Participants in the low adherence group viewed themselves as less involved in treatment decisions than participants in the high adherence group (see Table 3). Patients who rated themselves as more involved in treatment decisions (TES) reported fewer practical barriers, $r(1112) = -0.12$, $p < 0.001$. They also had fewer concerns about possible adverse effects of AEDs (AED Concerns), $r(1114) = -0.26$, $p < 0.001$, a stronger belief in their personal need for AEDs (AED Necessity) $r(1112) = 0.17$, $p < 0.001$, and were more positive about AEDs overall (AED NCD), $r(1092) = 0.15$, $p < 0.001$.

Can PAPA Variables Add to the Variance in Adherence to AEDs Explained by Demographic and Clinical Variables?

Hierarchical multiple logistic regression analysis (see Table 4) was conducted to test whether perceptual (AED Necessity and Concerns) and practical barriers (AED Practical Barriers) and perceptions of involvement in treatment decisions (TES) predicted adherence when controlling for clinical and demographic variables. When age, duration of epilepsy, seizure type, seizure frequency and number of different AEDs prescribed were forced into the model at Step 1, only a small proportion of the variance in adherence was predicted (See Table 4). Age of patients and the duration of their epilepsy were associated with adherence. The 60-84 year old age group reported the highest level of adherence. In addition, epilepsy duration also predicted a significant amount of the variance in adherence, with participants who reported that they had epilepsy for 4-10 years being at significantly higher risk of nonadherence than patients who reported that they had epilepsy for more than 20 years. Patients who were prescribed multiple AEDs reported higher adherence than patients who were on one AED. The Nagelkerke's R^2 of

0.07 for this step illustrated that although the model was significant, $\chi^2(15, N = 1144) = 52.64$, $p < 0.001$, the relationship between the predictors and adherence was not strong.

When we entered perceptual and practical barriers and involvement in treatment decision variables in Step 2 (AED Necessity, AED Concerns, AED Practical Barriers, TES), Nagelkerke's R^2 increased to 0.18 indicating a stronger relationship. Low adherence was associated with reduced necessity beliefs (AED Necessity) and increased reported practical barriers to medication taking (AED Practical Barriers). The relationship between AED Concerns and adherence was not significant in the multivariable model. Participants who reported more involvement in discussions about treatment were less likely to report low adherence.

Discussion

We found that nonadherence to AEDs was best understood in terms of how each individual interacted with their treatment. Patients' perceptions of their AEDs (necessity beliefs and concerns), their involvement in treatment decisions and their ability to deal with the 'practical' issues of taking daily medication as advised, were much more strongly related to nonadherence than clinical and demographic variables (including age, number of medications taken, seizure type and epilepsy duration).

Our findings are consistent with previous studies linking nonadherence to AEDs to patients' beliefs about AEDs (doubts about personal need for daily AEDs and concerns about potential adverse effects)[25; 38-41]. But they go further by assessing the value of other factors specified as potentially important in the NICE Medicines Adherence Guidelines[23]. This is the first study to measure the three variables that NICE considered most important for adherence (patients' beliefs and concerns, satisfaction with involvement in the treatment decision and 'practical' support with using medication) and quantify their relationship to AED adherence. In the univariable analyses, all these factors were significantly associated with adherence, and in the multivariable analysis practical barriers, doubts about necessity and satisfaction with involvement in treatment decisions all remained significant predictors, suggesting that all of these factors would need to be addressed in adherence interventions. Although the size of relationships between reported adherence and barriers to medication-taking were in the range of small-medium effects, we believe that these factors are still important for healthcare professionals to consider when supporting people with epilepsy. Reassuring patients regarding their medication and explaining why treatment with AEDs is needed may be a relatively quick, low risk and low-cost way of improving outcomes for patients. Concerns about medication have also been linked to reduced quality of life, and increased reporting of side effects. Addressing these barriers to adherence may therefore be of a wider benefit to patients.

As suggested within the NICE Medicines Adherence Guidelines[23], these relationships provide useful information for the development of adherence support interventions for epilepsy; by addressing doubts about need for AEDs, concerns about adverse effects and practical barriers to medication-taking, healthcare providers may be able to support people with epilepsy to adhere to AED treatments. Previous research (for systematic review see[14]) has suggested that intensive reminders and interactive interventions may be the most effective at improving adherence. Our results suggest this support might be more effective if it is tailored to address both perceptions and practicalities. To do this we need to look beyond the provision of 'practical support' designed to improve the patient's ability to adhere (e.g. reminders, clear instructions, simple regimens etc.), to consider the perceptual factors (e.g. beliefs about AEDs and involvement in treatment decisions) that influence the motivation to keep taking the treatment.

Reports of increased involvement in decisions about AED treatment were associated with higher adherence. This is reassuring, as it has been suggested that patients who feel that they have more choice over treatments may choose not to adhere[42]. Potentially, patients who are more involved in treatment decisions have more opportunity to express concerns and doubts about treatment to their physicians, and for these concerns and doubts to be addressed, with subsequent positive impact on adherence.

Beyond the effects on adherence, our findings suggested that many participants adhered to treatment despite concerns and doubts about their AED treatment. This was true even of our high adherence group who had an adherence score of greater than 44 (equivalent to saying that they 'sometimes' did 3 of the 10 nonadherent behaviours). More than half of the sample reported ambivalence about taking AEDs, expressing both high belief in their personal need for AEDs and high concerns about the potential negative effects of AEDs. Approximately 80% of participants reported at least one practical barrier to taking their AEDs. It is likely that these concerns and doubts, even if not affecting adherence, may affect other aspects of participants' response to their epilepsy. For example, patients' emotional response to treatment or relationship with their physician may be affected by unaddressed ongoing concerns.

There are several caveats to our findings. They are largely dependent on self-reported information; respondents may have misreported their diagnosis or adherence levels. The findings from the online sample are similar to those from the inpatient sample however, offering some reassurance from an inpatient sample who had a diagnosis of epilepsy confirmed by a specialist neurology team. To validate self-reported adherence, we attempted to compare AED blood levels with self-reported adherence (MARS scores) where these were available and found some evidence that these were associated. However, both assessments are limited. Self-report adherence measures have been validated against more objective measures of adherence, but patients may over-report adherence[34]. Likewise, AED blood level data may give a falsely pessimistic view of patients' adherence when AED half-life is short, or optimistic, in the case of 'white coat' adherence where patients increase medication intake immediately before a blood test. Even where accurate, MARS scores or AED levels may not correspond to clinical outcomes. Adherence is complex e.g. taking a certain combination of doses at particular times with/without certain foods, for a defined number of days. Particular types of nonadherence may drive clinical outcomes for epilepsy patients (e.g. missing 2 doses on consecutive days may have a greater effect than missing 1 dose/week for 2 weeks), and these could vary between patients or drugs (e.g. due to different absorption rates). We also cannot be certain that either the inpatient or online samples are representative of other epilepsy patients in general; we may have oversampled adherent patients who are more engaged with their care, or conversely patients who viewed it as an opportunity to express dissatisfaction with their treatment.

This survey was also cross-sectional and therefore we can show association but not prove that the PAPA variables or age/epilepsy duration caused nonadherence to AEDs. Some potentially unexpected relationships emerged; higher adherence in people who reported taking multiple AEDs than monotherapy, lower adherence in those with a more recent onset of epilepsy, a lack of association between seizure type and frequency and adherence. But, because the study is cross-sectional, we cannot draw firm conclusions regarding the causal relationships. For example, the link between epilepsy duration and adherence could indicate patients become more adherent to their medication over time, perhaps as they become more familiar and reconciled to their medication or develop habitual medication-taking routines. However, confounding factors, such as changes in prescribing patterns, may also contribute to this pattern of results. Likewise, people who have recent seizures or multiple medications may be receiving more healthcare support or perceive a greater need for treatment, and therefore have increased adherence. Longitudinal studies, tracing these variables over time, would be a more robust test of these relationships. These findings are reliant on participants accurately reporting their adherence, involvement in treatment decisions, and perceptual and practical barriers to adherence. We deliberately asked for very minimal information on demographic and other factors. For example, we did not collect data on educational level or ethnicity. It was felt that the questionnaire would be more acceptable to participants if we did not ask for this personal information. We acknowledge that this means that we cannot draw any conclusions about the generalizability of these findings across patients from different sociodemographic groups. Finally, given this and the sampling method (single site plus online) we cannot be sure whether the respondents were representative of people with epilepsy across the UK or beyond. It is likely that the sample may have contained, for example, patients who had more time to complete the survey, were more motivated to participate, or had better internet access than people who did not participate.

This study builds on previous evidence demonstrating the importance of concerns about AEDs and doubts about treatment need in explaining nonadherence in epilepsy and demonstrates that perceptual barriers and a lack of involvement in decisions about treatment are also barriers to adherence. Interventions to address doubts about perceived need for AEDs, concerns about adverse effects, and practical factors influencing medication taking may help epilepsy patients to better adhere to AEDs. There is a need to develop such interventions and test whether they are feasible, acceptable and effective methods of supporting people with epilepsy to adhere to their AEDs.

Key Points

- Low adherence was related to perceptual barriers: doubts about AED necessity, concerns about the potential adverse effects of treatment
- Low adherence was associated with perceptions of practical barriers to medication taking and lack of involvement in treatment decisions
- These factors had small to moderate effects on adherence, whereas reported clinical and demographic factors had very small effects
- Addressing concerns and doubts about AEDs, reducing practical barriers and engaging patients in treatment decisions may support adherence

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Disclosure of Conflicts of Interest

Sarah Chapman has undertaken consultancy for a UCL-business spin out company providing consultancy on medication-related behaviours to healthcare policy makers, providers and industry. The remaining authors have no conflicts of interest. 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

	n (%)
Age[a]	
Under 16 years	46 (4.1%)
16-24 years	174 (15.4%)
25-40 years	420 (37.3%)
41-59 years	384 (34.1%)
60-84 years	102 (9.1%)
Epilepsy duration[b]	
3 or fewer years	194 (17.3%)
4-10 years	254 (22.7%)
11-20 years	277 (24.7%)
more than 20 years	396 35.3%
Seizure frequency[c]	
about daily	155 (14.2%)
about weekly	221 (20.3%)
about monthly	360 (33.1%)
seizure free for more than a year	346 (31.8%)
Seizure type (seizures where I…)	
… am aware of what is happening	354 (31.4%)
… am confused or only partially aware	449 (39.8%)
… briefly lose consciousness	448 (39.8%)
…lose consciousness and jerk or convulse	683 (60.6%)

Table 1: Age, epilepsy duration and seizure characteristics.

Note. [a] 1 online participant missing from this analysis; [b] 3 online participants and 3 clinic participants missing from this analysis; [c] 38 participants missing from this analysis

	High adherence	Low adherence		
	n = 765	n = 355		
	m (sd)	m (sd)	d [95% CI]	
AED Necessity [a]	3.94 (0.73)	3.73 (0.89)	0.27 [0.14,0.39]	**t(577) = 3.90, p < .001**
AED Concerns [b]	3.16 (1.12)	3.35 (0.73)	-0.19 [-0.31,-0.06]	**t(995) = 3.45, p = .001**
AED NCD [a]	0.78 (1.25)	0.38 (1.19)	0.32 [0.20,0.45]	**t(1112) = 5.13, p < .001**
AED Practical Barriers [b]	11.70 (4.39)	9.61 (3.64)	0.58 [0.45, 0.70]	**t(589) = 7.78, p < .001**
TES	3.41 (0.70)	3.20 (0.79)	0.29 [0.16, 0.41]	**t(623) = 4.48, p < .001**

Table 2: PAPA variables in high and low adherence groups.

Note: [a] 5 participants missing; [b] 3 participant missing.

AED = antiepileptic drugs; NCD = Necessity-Concerns Differential; TES = Treatment Empowerment Scale

Predictor	**B**	**OR**	**R_N^2**
STEP 1: Demographic and Clinical Variables			**.064*****
Age			
Under 16 years	-0.57	0.56 [0.19, 1.67]	
16-24 years	-1.30	**0.27** [0.13, 0.59]**	
25-40 years	-1.18	**0.31** [0.15, 0.63]**	
41-59 years	-0.84	**0.43* [0.21, 0.88]**	
60-84 years	REF		
Epilepsy duration			
3 or fewer years	0.83	**2.30** [1.37, 3.86]**	
4-10 years	-0.15	0.86 [0.57, 1.30]	
11-20 years	0.19	1.21 [0.80, 1.81]	
more than 20 years	REF		
Seizure frequency			
about daily	0.12	1.12 [0.67, 1.88]	
about weekly	-0.42	0.66 [0.43, 1.01]	
about monthly	-0.20	0.82 [0.56, 1.19]	
seizure free for about 1 year	REF		
Seizure type (seizures where I...)			
... am aware of what is happening	-0.33	0.74 [0.54, 1.01]	
... am confused or only partially aware	0.04	1.04 [0.76, 1.43]	
... briefly lose consciousness	-0.05	0.95 [0.70, 1.29]	
...lose consciousness and jerk or convulse	-0.18	0.84 [0.62, 1.14]	
Medication regimen			
2 or more AEDs taken vs <2	0.38	**1.46* [1.06, 2.00]**	
STEP 2: PAPA variables			**0.178*****
AED Necessity	0.46	**1.58*** [1.30, 1.92]**	
AED Concerns	-0.22	0.80 [0.66, 1.45]	
Practical Barriers	-0.13	**0.87*** [0.84, 0.91]**	
TES	**0.23**	**1.26*[1.02, 1.55]**	

Table 3: Multiple logistic regression predicting adherence using the PAPA controlling for clinical and demographic variables at Step 1. Note.* p < .05, ** p < 0.01, *** p < 0.001; AEDs = antiepileptic drugs; TES = Treatment Empowerment Scale.

Figure captions

Figure 1: Attitudinal analysis of perceptions of AEDs.

Supplementary information Figure Captions

Figure S1: Proportion of respondents taking each AED. AEDs which fewer than 5% of patients were taking are omitted (pregabalin, phenobarbital, acetazolamide, gabapentin, primidone, eslicarbazepine, rufinamide, ethosuximide, vigabatrin, piracetam, stiripentol, tiagabine).

Figure S2: Percentages of respondents expressing doubts about their need for AEDs, as indicated by responding 'uncertain', 'disagree' or 'strongly disagree' on AED Necessity items.

Figure S3: Percentages of respondents expressing concerns about AEDs, as indicated by responding 'agree' or 'strongly agree' on AED Concerns items.

Figure S4: Percentages of respondents reporting experiences of practical barriers to taking AEDs, as indicated by responding 'rarely', 'sometimes', 'often' or 'always' on Practical Barriers items.

Figure S5: Percentages of respondents reporting experiences of involvement in decisions about treatment, as indicated by responding 'agree' or 'strongly agree' on Treatment Empowerment Scale items.

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