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Self-reported antiepilepsy medication adherence and its connection to perception of medication error

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ABSTRACT

Although 70% of people with epilepsy (PWE) achieve seizure freedom following an appropriate antiepileptic drug (AED) regime, evidence suggests that adherence to AEDs by PWE is suboptimal. Nonadherence to AEDs is associated with increased morbidity, mortality, emergency department visits, and hospitalizations, with reduced adherence also correlating to a lower quality of life, decreased productivity, and loss of employment. Furthermore, research indicates that medication errors which are widespread in chronic disease are less well studied in epilepsy but are likely also to contribute to avoidable disease morbidity and mortality.

The goals of this project were to determine rates of medication adherence by self-reported questionnaire and its links to perceived medication error in a cohort of PWE attending a general epilepsy outpatient clinic. Following a plan-do-study-act cycle, it was found that the most appropriate methodology for conducting was in the form of a bespoke 9-item self-administered questionnaire. One hundred eighty-six PWE completed a nine-question questionnaire asking patients about their own medication adherence habits and their perception that they were previously exposed to medication error.

This study found that 41% of respondents reported suboptimal adherence to AED therapy, while 28.5% of respondents self-reported that they unintentionally do not take their AED medication on an occasional, regular, or frequent basis. A 5.9% of respondents self-reported that they intentionally do not take their medication as prescribed. A 6% of respondents self-reported that they are both unintentionally and intentionally nonadherent to their AED therapy. No significant associations were demonstrated between age, sex, perceived effectiveness of medication, feelings of stigma/embarrassment, adverse effects or additional neurological comorbidities, and unintentional or intentional nonadherence.

A 28.5% of respondents to the questionnaire reported that they perceived themselves to have been subjected to medication error. Prescribing errors were the most common form of perceived medication error, followed by dispensing errors, then administration errors. Significant associations were found between ineffective medication and feelings of stigma or embarrassment about epilepsy with perceived prescribing errors. Intentional nonadherence to medication was significantly associated with perceived dispensing errors.

1. Introduction

Medication adherence is defined as the extent to which a person takes their medication as prescribed with respect to dosage and dosing intervals [1]. Nonadherence to medication can take many different forms (see Table 1).

Despite almost 70% of people with epilepsy (PWE) being able to achieve seizure freedom following an appropriate antiepileptic drug (AED) regime, research evidence suggests that between 29% and 66% of PWE are nonadherent to their prescribed medication [2,3]. Nonadherence to AEDs is associated with increased emergency department visits, hospitalizations, fractures, and head injuries [2,4]. Reduced adherence also correlates with lower quality of life, decreased productivity, seizure-related job loss, and seizure-related motor vehicle accidents [5]. Seizure risk is 21% higher in nonadhering PWE when compared with those who adhere, and they exhibit reduced seizure control [2,6]. The most serious impact of epilepsy is death, whether through accidents, trauma, or the syndrome known as sudden unexpected death in epilepsy (SUDEP) [7]. Epilepsy mortality has been associated with failure to collect repeat prescription for epilepsy medication [8].

Abbreviations: PWE, people with epilepsy; AED, antiepileptic drug.

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Table 1
Definitions of medication adherence, medication nonadherence, and the three categories of medication error.

Medication adherence	The extent to which a person takes their medication as prescribed with respect to dosage and dosing intervals [1]
Medication nonadherence	Involves reduced or increased amount of a single dose, decreased or increased amount of daily doses, extra dosing, incorrect dosing intervals, a lack of awareness of the need for medication, taking duplicate or discontinued medication, and regularly forgetting or intentionally not taking medication [12].
Prescribing error	Incorrect drug selection for a patient, be it the dose, the strength, the route, the quantity, the indication, or the contraindication [13].
Dispensing error	Discrepancy between a prescription and the medicine that the pharmacy delivers to the patient or distributes to the ward on the basis of the prescription [14].
Administration error	Discrepancy between the drug therapy received by the patient and the drug therapy intended by the prescriber [15].

From a health economics perspective, nonadherence can involve additional costs to the healthcare service because of the extra staff and resources required to deal with additional hospital admissions caused by seizures and seizure-related injuries [9]. Data indicate that all medication nonadherence across European Union health systems costs governments an estimated €125 billion and contributes to the deaths of nearly 200,000 Europeans annually [10].

Medication errors are defined as any error occurring in the medication use process from prescribing to dispensing to administration of an inappropriate or incorrect drug or dose irrespective of whether such errors lead to adverse consequences [11]. As the definition suggests, errors can occur at any stage in the drug use process; however, medication errors can be broadly categorized into three different types: prescribing, dispensing, or administration errors (see Table 1).

While the issue of medication adherence in patients with epilepsy has been acknowledged and relatively well explored, the issue of medication errors relating to AEDs and the impact on patients and families is less well understood [16–18]. In this study, the concept of PWE feeling/perceiving that they were exposed to a medication error and how this might influence their AED compliance behaviors was explored.

In terms of continuous quality improvement in clinical epilepsy care, promoting AED adherence and reducing medication errors are important activities. Prior to designing interventions to increase AED adherence and reducing medication errors, the Epilepsy Department of St. James's Hospital (SJH) wanted to establish baseline data surrounding adherence behaviors and perception of medication error using clinical audit. A number of established instruments measuring self-reported medication adherence exist such as the Morisky medication adherence scale – 8 (MMAS-8), the medication possession ratio (MPR), and the epilepsy self-management scale (ESMS). Rather than using one of these instruments, a unique questionnaire was developed for this audit as we wished to include questions about perception of medication error.

2. Methods

The audit was carried out in the form of a self-administered questionnaire. The questionnaire investigated the influence of eight factors – sex, age, number of medications, current perceived effectiveness of medication, prior perceived effectiveness of medication, perceived adverse effects, perceived stigma, and additional neurological comorbidities – on whether a PWE intentionally or unintentionally was nonadherent to AEDs through a self-reported questionnaire.

2.1. Study design

Initially, the idea of the audit being carried out as an oral interview by the epilepsy staff was considered. The interaction would take place in an interview style, with the nurse asking a series of 20 questions to the participant in a conversational manner and recording their answers. This methodology was trialed during the first two weeks of the study. This was seen to place a heavy burden on already strict time constraints, and two further PDSA cycles were undertaken. This resulted in the creation of a nine-question self-administered survey completed in the waiting room, recording self-reported medication adherence and perceived exposure to medication error. (See Fig. 1)

The questionnaire (see Appendix 1) included questions about the patient's current AEDs, rate of forgetting to take medication, intention to adhere to AEDs, belief in effectiveness of medication, experience of AED adverse effects, feelings of epilepsy-related stigma, comorbidities, and perception of being subject to prescribing, dispensing, and administration errors. The questionnaire provided options to select coded responses as well as facility for respondents to provide free-text comments. The questionnaire was paper-based and was designed to be self-administered by patients while they were in the waiting area of the general epilepsy outpatient clinic.

2.2. Setting, participants, and data collection

This study was carried out in the epilepsy division of the Department of Neurology, SJH, Dublin, Ireland between January and October 2018.

There is one general epilepsy clinic per week run by the service. This clinic serves to provide chronic disease management in a population of 2500 established PWE. A presenting sample of PWE who attended a weekly outpatient epilepsy clinic were invited to complete the questionnaire. All established PWE over the age of 18 who were prescribed AEDs and attend this clinic were eligible for inclusion in this study.

Participants were approached prior by a member of the epilepsy care team while they were in the waiting room of the outpatient clinic to their appointment. The epilepsy team member provided general information about the study; how it was intended to develop an intervention for driving improvement of medication adherence and safety; and before the content of the questionnaire was explained. Where relevant, a friend/relative/carer who accompanied the patient to the clinic was asked to complete the questionnaire on the patient's behalf.

Information on whether the respondents unintentionally were nonadherent to their medication was determined from responses to the question 'How often do you forget to take your medication?'. Respondents could choose between the following alternative answers to this question: 'never', 'occasionally', 'regularly', and 'frequently'. Information on whether the respondents were intentionally nonadherent to AEDs was determined from responses to the question 'Have you ever intentionally not taken your medication as prescribed?'. Respondents could answer 'yes' or 'no' to this question, and if they answered 'yes', they were asked to report the reasons for such nonadherence. In addition, respondents could provide could provide comments in a free-text section at the end of the questionnaire.

Information on whether respondents perceived that they had been exposed to a form of medication error was determined from responses to the following question 'As far as you are aware, have you ever been subject to any of the following medication errors: (i) Prescribing Error (Incorrect selection of drug/dose/strength/route by prescribing doctor), (ii) Dispensing Error (Incorrect drug dispensed by pharmacist), or (iii)

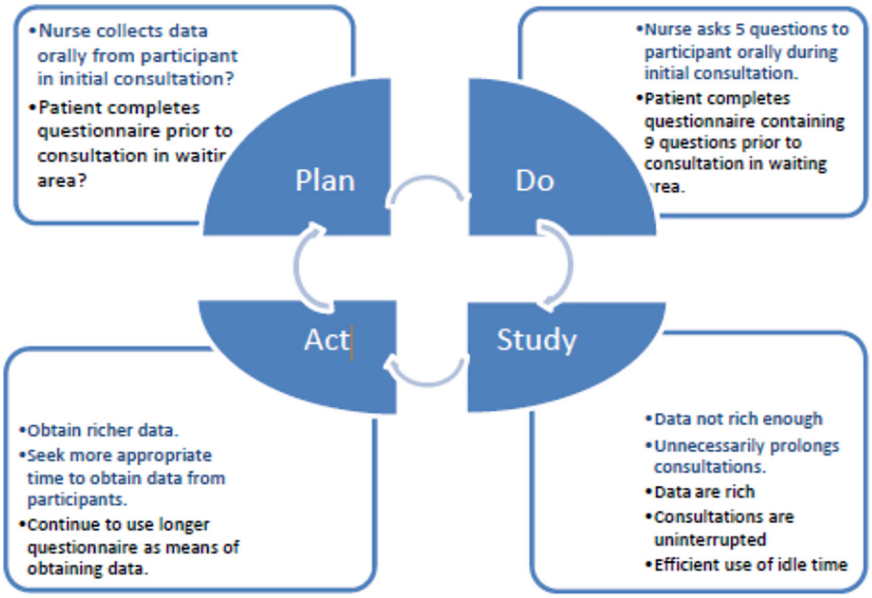

Fig. 1. Outline of Plan-Do-Study-Act (PDSA) cycle utilized to optimize clinical audit methodology.

Administration Error (Drug taken incorrectly by patient or administered improperly to patient)?'. Respondents could answer 'yes' or 'no' to these questions.

2.3. Data analysis

There were eight independent variables that were tested for unintentional and intentional nonadherences: sex, age, number of current AED medications prescribed, current perceived effectiveness of medication, previous perceived effectiveness of medication, perceived adverse effects of medication, experiencing stigma/embarrassment about epilepsy, and presence of additional neurological comorbidities.

Each of these eight independent variables was also tested for perception of exposure to prescribing errors, dispensing errors, and administration errors among participants. Unintentional and intentional nonadherences were also tested for exposure to each of these forms of medication error, i.e., is there a relationship between nonadherence to medication and exposure to medication errors?

Microsoft Excel and IBM Statistical Package for the Social Sciences (SPSS) were used to conduct data analysis. To test possible group differences, Pearson's chi-squared tests were performed. $P < 0.05$ is

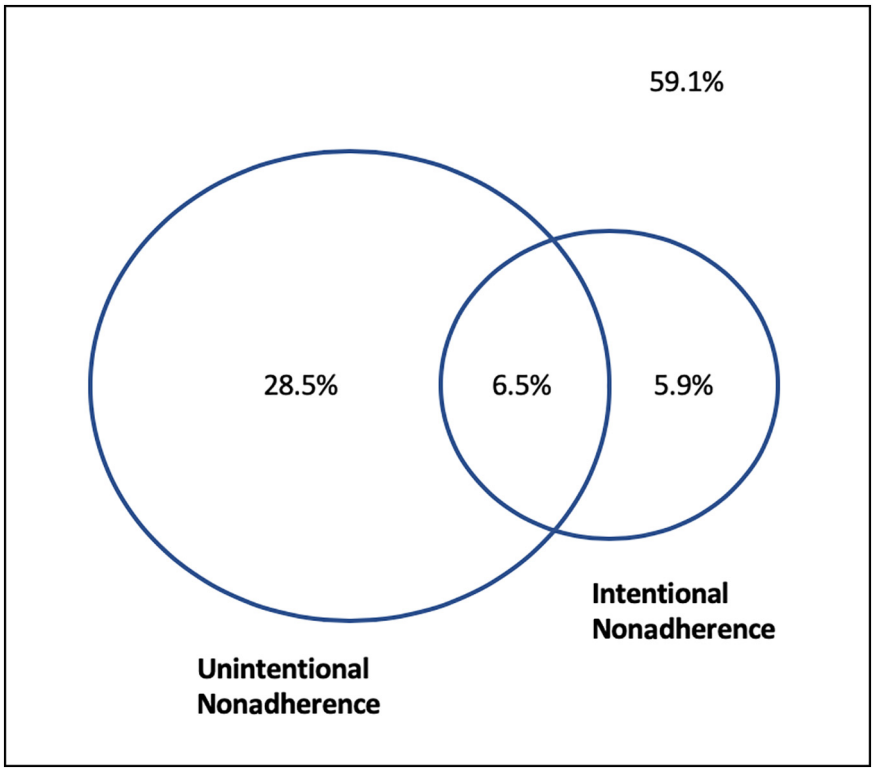

Fig. 2. Diagram illustrating self-reported adherence to AEDs across all respondents (n = 186).

Table 2
Table displaying the p value associations between eight different factors and whether respondents self-reported unintentionally or intentionally not adhering to AEDs (n = 186).

	Unintentional nonadherence	Intentional nonadherence
Sex	0.267	0.825
Age	0.296	0.251
Number of AEDs	0.281	0.536
Unintentional nonadherence	–	0.106
Intentional nonadherence	0.106	–
Current perceived effectiveness of medication	0.057	0.464
Previous perceived effectiveness of medication	0.758	0.656
adverse effects	0.356	1.000
Experiencing stigma or embarrassment about epilepsy	0.224	0.241
Presence of neurological comorbidity	0.895	0.777

considered statistically significant. P values were subject to the Bonferroni correction where possible.

2.4. Ethics

This study was classified as a Clinical Audit by the SJH Research Department. Surveying patients about their medication did not require referral to a full institutional ethical board review but was subject to the local clinical governance rules covering clinical audit.

3. Results

3.1. Medication adherence

During the study period, 186 PWE completed the questionnaire. A 59.1% of patients reported no medication adherence issues while a 40.9% of respondents fail to adhere optimally to prescribed AEDs. The results suggested that medication adherence was more often unintentional than intentional.

A 28.5% of respondents self-reported that they ***unintentionally*** forget to take their medication on an occasional, regular, or frequent basis. A 5.9% of respondents admitted to ***intentional*** nonadherence to AED's. A 6.5% of respondents stated that they have both unintentionally forgot and intentionally did not take their prescribed AEDs in the past (See Fig. 2).

No significant ($p < 0.05$) associations were demonstrated when a chi-squared test was used to compare whether eight different factors influenced respondents' self-reported unintentional or intentional nonadherence to AEDs (see Table 2). None of sex, age, number of AED's prescribed, current perceived effectiveness of medication, previous perceived effectiveness of medication, perceived adverse effects, experiencing stigma or embarrassment about epilepsy, or the presence of additional neurological conditions appeared to influence whether respondents unintentionally or intentionally nonadherent to AED therapy.

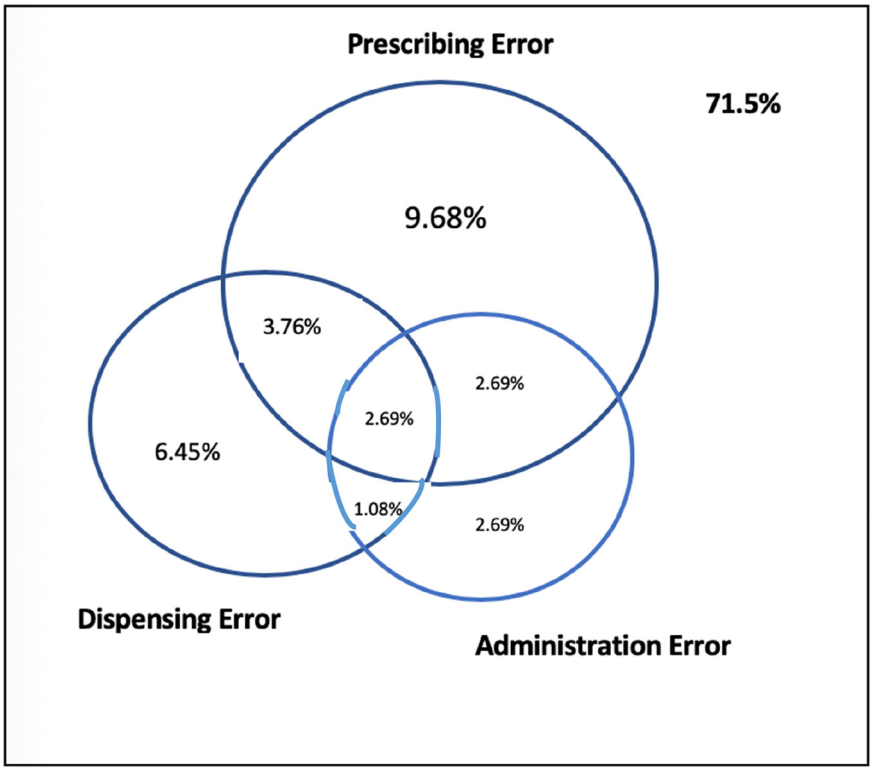

Fig. 3. Breakdown of medication errors reported by respondents (n = 186).

Table 3
Table displaying significant ($p < 0.05$) p value associations between patient factors and whether respondents self-reported being exposed to a prescribing error. ($n = 186$).

	Have you ever been subject to a prescribing error?
Effectiveness of current medication	0.004
Experiencing stigma/embarrassment	0.041
Exposed to dispensing error	<0.001
Exposed to administration error	<0.001

3.2. Medication errors

Of the 186 participants, 28.5% of respondents reported a perceived medication error. Prescribing errors (18.81%) were the most common form of perceived error reported by this cohort of PWE, followed by dispensing errors (14%), then administration errors (9.15%). A small number of PWE perceived that they were subject to some combination of 2 or 3 different forms of medication error (see Fig. 3).

Significant ($P < 0.05$) associations were seen between four factors and perception of exposure to prescribing errors: poorer perceived effectiveness of current AED medication, experiencing stigma or embarrassment because of epilepsy, self-reported exposure to dispensing errors, and self-reported exposure to administration errors (Fig. 3). This information is summarized in Table 3.

Significant ($P < 0.05$) associations were seen between three factors and perception of exposure to dispensing errors: intentional nonadherence to AED medication, perception of exposure to prescribing errors, and perception of exposure to dispensing errors. This information is summarized in Table 4.

Significant ($P < 0.05$) associations were seen between three factors and self-reported exposure to administration errors: unintentional nonadherence to AED medication, self-reported exposure to prescribing errors, and self-reported exposure to dispensing errors. This information is summarized in Table 5.

4. Discussion

The major findings of this study were that 40.9% of respondents to a self-administered questionnaire reported suboptimal adherence to AEDs, 28.5% perceived that they were subject to a medication error, and patients who perceive errors to be occurring are less adherent than those who do not.

In previous studies examining the reasons for nonadherence to AEDs, 'forgetfulness' appeared as the main self-reported reasons for nonadherence to medication [10,19]. This study is no different, with unintentional nonadherence reported by 35% of all participants compared with 12.4% of respondents who reported intentional nonadherence to medication. A recent study by Henning et.al utilized an anonymous online questionnaire to question PWE about their medication habits and found that 40% of PWE 'sometimes' or 'often' forgot to take their medication [20]. The same study reported that 30% of PWE intentionally did not follow the treatment plan with their physician. The different intentional nonadherence rates reported in this study and Henning et. al's study could be explained by the lack of anonymity in our survey.

Previous studies examining medication adherence rates across populations of PWE have predominantly used methods such as the MMAS, the MPR, and the ESMS [21–23]. Our PDSA cycle informed the researchers that a short, bespoke self-administered questionnaire including questions relating to perceived error, extending the time scale for data beyond 2 weeks, was the most appropriate methodology for conducting this first pass audit. Such a tool has not been used in this population previously. The overall nonadherence rate of 41% obtained in this study via self-report lies within the nonadherence rates of 29–66% among adult PWE reported in a recent systematic review by O'Rourke and O'Brien [3].

No significant links were found between sex, age, number of medications, current perceived effectiveness of medication, previous perceived effectiveness of medication, experiencing stigma or the presence of additional neurological conditions, and nonadherence to medication. This demonstrates the complexity of nonadherence to AEDs, and undoubtedly, there are several reasons behind a patient's decision not to take their medication as prescribed. This points us to the idea that nonadherent behavior is a dynamic process with many psychosocial, physical, cognitive, and personal factors involved, evidence for which is provided in Smithson et al.'s 2012 study which sought to identify at risk PWE for medication nonadherence [24]. Despite the many reports of the prevalence of nonadherence and complex causation in epilepsy care, there are few studies of interventions to address this issue. While nonadherence is problematic in all chronic conditions, one might argue that the consequences in epilepsy care may have more wide ranging physical and psychosocial consequences given the unpredictable nature of seizures.

To our knowledge, this is the first study that explores rates of perception of medication errors in a cohort of adult PWE. The number of participants who believed that they were subject to all three forms of medication error was high – 18.8% of participants perceived that they were subject to a prescribing error, 14% believed that they were subject to a dispensing error, and 9.1% felt that they were subject to an administration error. As this study did not set out to measure the rate of "actual" medication error, the veracity of the PWE error perception is not known. Furthermore, it is challenging to assess and compare these rates with other studies examining medication errors across epilepsy, neurological disease, or chronic disease in general given the lack of research in this area. A recent systematic review highlighted the lack of uniformity in examining medication errors and error-related adverse event rates in primary care and ambulatory settings. Across 60 different studies, medication error prevalence

Table 4
Table displaying significant ($p < 0.05$) p value associations between patient factors and whether respondents self-reported being exposed to a dispensing error. ($n = 186$).

	Have you ever been subject to a dispensing error?
Intentional nonadherence to medication	0.035
Exposed to prescribing error	<0.001
Exposed to administration error	0.002

Table 5
Table displaying significant ($p < 0.05$) p value associations between patient factors and whether respondents self-reported being exposed to an administration error. ($n = 186$).

	Have you ever been subject to an administration error?
Unintentional nonadherence to medication	0.035
Exposed to prescribing error	<0.001
Exposed to dispensing error	0.002

estimates ranged from 2% to 94% [25]. We assume that there are important differences in patient perception of medication error and true and validated errors. Exploring medication diaries, reconciliation reports, and pharmacy records to obtain these data was beyond the scope of this clinical audit. Nonetheless, understanding perception of medication errors is important in understanding where patients feel their service can improve, which was the aim of this project with respect to continuous quality improvement in epilepsy care.

Analysis showed that respondents who perceived exposure to one type of medication error were significantly more likely to believe that they had been exposed to the other two forms too. This tells us that it is likely that respondents who believe that medication errors are occurring along their medication use process are likely to believe that they are occurring at multiple stages, not solely at the prescribing, dispensing, or administration stage. The significant association between respondents perceiving current medication to be not effective and perceiving prescribing errors is interesting and suggests that ineffectiveness of AEDs could be linked to prescribing errors by clinicians. The association between intentional nonadherence to medication and perceived dispensing errors suggests a putative link between dispensing errors by pharmacists and PWE intentionally not taking their medication as prescribed. Patient perception may give rise to their belief that the prescriber or pharmacist is responsible for medication error leading to their sense of victimization and consequent reduced compliance with AED treatment. A next step for this research will involve developing an audit tool for monitoring adherence and error data, in addition to generating a 'true' sample of medication adherence rates through interrogation of prescription refill data and diaries. Prospectively looking at participants who reported intentional nonadherence to medication or perceived exposure to medication errors and qualitatively examining the reasons for their perception of these phenomena will also occur.

Increased accountability for medication error and safety is leading to more studies such as this one where individual patient factors are being assessed to determine which patients are at most risk of being subject to a medication error. A number of solutions have been proposed to minimize the impact of medication errors. A systematic review of 38 studies of primary care interventions designed to reduce medication-related adverse events found that the most successful interventions included a medication review conducted by a pharmacist or another clinician [26]. The impact of medication safety education with both healthcare providers and patients on reducing medication error rates has been reviewed. It was found that educational interventions may impact on clinician adherence to prescribing guidelines [27]. Another review found that patient self-administration of medication can be seen as safer than usual care following appropriate education and preparation [28]. An eHealth solution to improve medication safety has also been reviewed. Computerized provider order entry (CPOE), a clinical decision support system, is designed to alert clinicians of inappropriate medications. In a review of 10 randomized control trials of CPOE, a reduction in medication errors was found in only half of the studies [29].

5. Limitations

There are a number of limitations associated with this study.

Initially, it was envisaged that a mixed methods approach would be used to investigate medication adherence and medication errors in this population, similar to Smithson et al. [24]. A methodology where semi-structured interviews were conducted by clinicians during clinical appointments was trialed for a two-week period. It was seen to prolong appointments and place a burden on already strict time constraints given the large number of patients who attend the weekly clinics. This meant that a new methodology was required, leading to the design of a questionnaire.

Logistically, the questionnaire proved effective in allowing as many patients as possible to take part in the study as it could be completed while they were seated in the waiting area of the clinic. The self-reported nature of the questionnaire was suitable for this study as it was examining what the participants testify about their medication adherence and their perception of exposure to medication errors. Although the questionnaire designed specifically for this study was invalidated, it is important to note that overall observed nonadherence rate of 41% among participants lies within the 29–66% rate for adult PWE reported in a recent systematic review by O'Rourke and O'Brien and suggests a reliability of the questionnaire instrument.

Data were collected at a specialist outpatient clinic at SJH, Dublin, Ireland. After a period of approximately nine months, it was found that almost all patients attending these clinics had either completed the questionnaire at a previous clinic or declined to take part. Opting to collect data from one clinical setting limited the number of potential participants in this study and led to data saturation occurring with less than 200 participants over the time scale of the project.

6. Conclusions

Nonadherence to AEDs by PWE likely stems from a combination of personal, medical, and psychosocial issues. A number of PWE believe that errors are being made in the medication use process, particularly at the prescribing and dispensing stages. People with epilepsy who perceive that they have been subject of a medication error are significantly more likely not to adhere to AEDs. These findings open the door to future research being conducted with PWE to evaluate their attitudes and behaviors towards epilepsy treatment and the healthcare professionals that provide it. It also suggests the urgent need to consider interventions that are institutional, educational, electronic-enabled, and others that might mitigate these numbers.

Declaration of competing interest

None of the authors in this paper have competing interests which could inappropriately bias this study.

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Appendix 1. Questionnaire

Medication Adherence Questionnaire

A study is being carried out within the Neurology department of St. James's Hospital investigating medication adherence and medication errors in patients. We would be very grateful if you would take part.

Personal Details (If you are a friend/relative/partner/carer please provide the patient's details below)

Name: _____ Gender: _____

Age: _____

If you have attended the Epilepsy Clinic more than once and are happy to participate in the study, please answer the following questions (Circle your choice unless prompted to do otherwise)

1. How many epilepsy medications are you currently taking? _____

Please list all epilepsy medications you are currently taking in the box below.

2. How often do you forget to take your medication or miss a dose? (Place a tick beside the most appropriate answer)

- Never
- Occasionally (Once every 2-4 weeks)
- Regularly (More than once every 2 weeks)
- Frequently (More than once every week)

3. Have you ever intentionally not taken your medication as prescribed? Yes No

If yes, why so? _____

4. How effective do you believe your current medication is at controlling seizures?

Very effective Somewhat effective Not effective

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