The influence of demographics and comorbidity on persistence with anti-seizure medication

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ABSTRACT

Purpose: To examine the rate of persistence with anti-seizure medications (ASMs) in a cohort of patients with epilepsy, and to investigate the impact of a range of clinical and demographic factors on persistence

Methods: Patients receiving ASMs for epilepsy were identified from linked, routinely collected data within the NHS Greater Glasgow and Clyde health board area between January 2011 and August 2019. Persistence with individual ASMs at 365-days after initiation was assessed using a 90-day allowable gap between individual prescriptions. Univariate logistic regression was used to estimate the association between 1-year persistence with ASM and demographic characteristics, comorbidities, and medication characteristics.

Results: In total, 6,449 patients with epilepsy were identified – 1,631 were new users of ASMs at baseline and 4,818 had been prescribed at least one ASM prior to baseline. Persistence with individual ASMs ranged 11.8% to 78.6%. Persistence was significantly lower in younger patients and patients who had previously been non-persistent to ASMs. Persistence was higher amongst those with cardiac comorbidities, previous stroke, or higher overall comorbidity, as well as those prescribed newer ASMs.

Conclusion: Persistence varied widely. Demographic factors, previous non-persistence and overall number of comorbidities were more important determinants of persistence to anti-seizure medications than specific individual comorbidities. Interventions to improve persistence should be targeted at younger patients from more deprived backgrounds and those who have previously been non-persistent with ASMs.

1. Introduction

Epilepsy is among the most common neurological disorders, affecting an estimated 50 million people worldwide [1]. The National Institute for Health and Care Excellence (NICE) estimated the prevalence of active epilepsy (i.e. patients with continuing seizures or continued need for treatment) in the UK to be 500–1000 cases per 100,000 population, and the incidence of newly diagnosed epilepsy to be 50 per 100,000 population per year [2].

Epilepsy is most frequently managed through the use of anti-seizure medications (ASMs); the specific treatment plan typically taking into account the patient’s seizure type, syndrome, comorbidities, and concomitant medications. Around two-thirds of patients achieve seizure freedom early in the course of their condition through the use of ASMs [2]. Patients not attaining control will require further ongoing modifications under clinical supervision.

Gaining good seizure control is important, since recurrent seizures are associated with reduced quality of life, reduced employment and education, and higher risk of injury and death [3,4]. Poor engagement with the therapeutic process is a frequent cause of poor seizure control, and ensuring patients are taking the recommended ASM should be a mainstay of the management of epilepsy [5]. Identifying when patients are not persistent is difficult and poor persistence will not always be recognised in the clinic. Identifying risk factors associated with poor persistence allows health care professionals to design services to meet the needs of those at highest risk to reduce the risk associated with poorly controlled epilepsy.

Persistence to a medication can be measured as the length of time between first prescription and the discontinuation of treatment with that medication [6]. Patient persistence to ASMs reflects both their efficacy and tolerability. Studies have identified several potential factors associated with ASM persistence and discontinuation. The use of older ASMs

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such as carbamazepine, valproate and phenytoin has been shown to be associated with shorter persistent time and higher risk of discontinuation compared to newer ASMs such as levetiracetam and lamotrigine [7]. Additionally, one study highlighted that persistence was higher where ASMs were taken as monotherapy than as part of polytherapy [8].

People with epilepsy have been shown to have greater levels of comorbidity than the general population [9,10], but the influence of comorbidities on persistence to ASMs is not fully elucidated. Understanding the clinical or demographic features associated with non-persistence to ASMs may help improve the therapeutic partnership between people with epilepsy and their clinicians, allowing clinicians to provide a service that meets individual needs.

By utilising routinely generated health data from a validated regional epilepsy register, we aimed to examine the rates of persistence with different ASMs and to examine the impact of different demographic and clinical factors on persistence. We assessed persistence among those who recently commenced ASM therapy (‘new users’) as well as those who had been on long-term treatment for epilepsy (‘existing users’).

2. Methods

2.1. Study population

Each individual registered with a primary care practitioner in Scotland has a unique ten-digit community health index (CHI) number. This is appended to all health-care encounters within NHS Scotland services and allows linkage of routinely collected data related to the same individual. Patients who attended hospitals in NHS Greater Glasgow and Clyde (NHS GGC) between January 2011 and August 2019 inclusive were identified. Patients were included if they had attended the regional neurology center as an outpatient and/or had an epilepsy-related inpatient hospitalisation or admission to A&E and were dispensed at least 1 prescription for an ASM over the study period. Patients who were younger than 16 years at baseline or had only ever been prescribed gabapentin monotherapy during the study period were excluded. Patients were censored if they died or moved out of the NHS GGC health board area during the study period, identified through National Records Scotland (NRS) death records and data confirming patient registration with an out of health board GP, respectively.

2.2. Definition of exposure, outcome, and covariates

The demographic factors of interest were age, sex, and area-based socioeconomic status at baseline. Age was treated as an ordinal variable and Scottish Index of Multiple Deprivation (SIMD) was derived from postcode of residence and converted into general population quintiles.

ASMs were defined as those compounds appearing in sub-section 04.08.01 of the British National Formulary (BNF). Patients were classified as new users of ASMs if they did not have a dispensed ASM in the year prior to their index date. Existing users were classified as previously non-persistent if they had no ASM prescriptions within the 90 days prior to their index date. Patients were classified as being dispensed ASM monotherapy or combination therapy at baseline based on whether they were dispensed one ASM or two or more ASMs on their index date. The primary outcome of interest in this study was persistence at 365 days after initiation. Persistence to ASMs was inferred if there was a gap between prescriptions of less than 90 days, with rates of persistence determined for each medication and summarised for the whole cohort and for the sub-groups described above. The 90-day allowable gap between prescriptions was chosen based on 30- or 60-day supply of ASMs per prescription being the most common, and to allow for a level of non-adherence. Only patients’ first periods of persistent use for each medication were considered. For patients dispensed at least one additional medication during follow-up, their first additional medication was classified as an add-on therapy if their duration of polytherapy exceeded 90 days, and a switch from their index medication if there was an overlap of less than 90 days or no overlap.

Comorbidities were identified at baseline using hospitalisation, general practice, and dispensing records during the one-year period before the patient’s index date (see Appendix 1 - Definition of morbidity). Comorbidity count was calculated as the number of individual medications (not including ASM) that the patients received during the one-year lookback period and only included medication where there was at least 90 days between the first and last prescription. The characteristics of each ASM were used as covariates, including generation (three categories based on date of licensing), potential for neuropsychiatric side-effects (defined as yes or no), and mechanism of action (dichotomised into sodium channel blocking or other) (Table A3).

2.3. Statistical analyses

Statistical differences between new and existing users were identified using t-tests for continuous variables and chi-2 tests for categorical variables. Univariate logistic regression analysis based on generalised estimating equations (GEE) was used to estimate the association between one-year persistence to ASMs and demographic factors, comorbidities, previous non-persistence to ASM, and medication characteristics. A separate, univariate sub-group analysis of patients prescribed ASMs with neuropsychiatric side effects (Table A3) to determine if there was a significant difference in persistence to these drugs in patients with and without mood disorders at baseline.

Only patients who were new users of ASMs or previously non-persistent existing users who were starting new periods of treatment after a period of 90 days with no prescriptions were included in this. All analyses were conducted in R 3.5.0 using RStudio v1.1.453.

3. Results

Between January 2011 and August 2019, 10,742 people with epilepsy attended NHS GGC outpatient clinics or A&E departments with a clinical code for epilepsy. Of these patients, 6449 received at least one prescription for ASM during the study period. At baseline, 1631 (25.3%) patients were new users of ASM and 4818 (74.7%) had received a prescription for an ASM in the previous 12 months. Of the existing users, 713 (14.8%) were previously non-persistent at baseline, with the remaining 4105 (85.2%) continuing a previous period of persistent use of at least 1 ASM. At baseline, 5055 (78.4%) of the whole cohort were prescribed one ASM, 1058 (16.4%) were prescribed two and 336 (5.2%) were prescribed three or more. The median length of follow-up was 7.37 years.

There were significantly more female patients who were existing users of ASMs at baseline than were new users, and there were significant differences between the two groups of patients in both age and SIMD. Length of follow-up was significantly longer for existing users than new users.

3.1. Demographics

Patient demographics are outlined in Table 1. The mean age at baseline was 52.7 years. More than half (52.6%) of PWE were in the most deprived quintile of the general population.

3.2. Comorbidity

At baseline, 33.8% of PWE had at least one comorbid chronic condition and thus can be defined as having multimorbidity and 22.6% had at least two comorbidities. Details of additional comorbidities are shown in Table 2.

The most common physical health comorbidities were hypertension and asthma. One of the most striking findings is the frequency of mental...
health and/or substance-related comorbidities in PWE. Forty eight percent (48%) of PWE met the definition for depression during follow-up, with 31.5% classified as having significant anxiety. Addictions were also increasingly recognised amongst all cohort patients across the duration of follow up, with alcohol dependence noted in 19.1% and other psychoactive substance abuse in 7%.

Amongst new users there were significantly more patients with higher overall comorbidity than amongst the existing users. Additionally, there were a higher proportion of new with atrial fibrillation, previous stroke, chronic kidney disease, liver disease, depression, bipolar disorder and substance abuse, and a lower proportion of new users with asthma, cancer, coronary heart disease, anxiety and learning difficulties compared to existing ASM users at baseline.

4. New user persistence

4.1. Overall persistence

Of the 1631 new users, 736 (45.1%) were persistent with the index ASM at 12 months. One hundred and sixty-one (9.9%) new users did not persist with any medication for at least 365 days during the study period. Of these non-persistent patients, 143 were never prescribed any alternative medications.

Seven hundred and fifty-seven (46.4%) new users were prescribed at least one additional medication during the study period, with an even split in the first additional drugs between continuation of the index therapy alongside the new medication (n = 377) and replacement of the index therapy with the new medication (n = 380).

The persistence rates with additional ASMs were similar, with around 40% of PWE continuing therapy at 365 days (Table 3).

4.2. New user prescribing and persistence to ASM

Among the 1631 new users the most commonly prescribed monotherapy was levetiracetam (n = 559, 34.3%) followed by lamotrigine (n = 389, 23.9%). Persistence ranged from 25.7% for topiramate to 78.6% for lacosamide (Fig. 1).

Table 1
Demographic characteristics of cohort as a whole and patients split into new and existing users of ASMs at baseline.

|                | All patients (N = 6449) | New users (N = 1631) | Existing users (N = 4818) | p   |
|----------------|-------------------------|----------------------|--------------------------|-----|
| Gender         |                         |                      |                          |     |
| Female         | 2977 46.2%              | 692 42.4%            | 2285 47.4%               | <0.001 |
| Male           | 3472 53.8%              | 939 57.6%            | 2533 52.6%               |     |
| Age (years)    |                         |                      |                          |     |
| 16–19          | 186 2.9%                | 69 4.2%              | 117 2.4%                 | <0.05 |
| 20–29          | 633 9.8%                | 205 12.6%            | 428 8.9%                 |     |
| 30–39          | 796 12.3%               | 229 14.0%            | 567 11.8%                |     |
| 40–49          | 1196 18.6%              | 273 16.7%            | 925 19.2%                |     |
| 50–59          | 1.261 19.6%             | 261 16.0%            | 1000 20.8%               |     |
| 60–69          | 1072 16.6%              | 227 13.9%            | 845 17.5%                |     |
| 70–79          | 825 12.8%               | 195 12.0%            | 630 13.1%                |     |
| 80–89          | 478 7.4%                | 172 10.5%            | 306 6.4%                 |     |
| SIMD           |                         |                      |                          |     |
| 1 (most deprived) | 3390 52.6%           | 826 50.6%            | 2564 53.2%               |     |
| 2              | 1122 17.4%              | 309 18.9%            | 813 16.9%                | <0.05 |
| 3              | 834 12.9%               | 201 12.3%            | 633 13.1%                |     |
| 4              | 564 8.7%                | 165 10.1%            | 399 8.3%                 |     |
| 5              | 539 8.4%                | 130 8.0%             | 409 8.5%                 |     |

Table 2
Frequency of comorbidity at baseline for the full cohort and for new and existing ASM users.

| Condition                  | All patients | New users | Existing users | p   |
|---------------------------|--------------|-----------|----------------|-----|
| Asthma                    | 1289 20.0%   | 279 17.1% | 1010 21.0%     | <0.05 |
| COPD                      | 514 8.0%     | 120 7.4%  | 394 8.2%       | 0.4  |
| Cancer                    | 193 3.0%     | 16 1.0%   | 118 2.5%       | <0.05 |
| Hypertension              | 1540 23.9%   | 359 22.0% | 1181 24.6%     | 0.09 |
| Coronary heart disease    | 568 8.8%     | 116 7.1%  | 452 9.4%       | <0.05 |
| Atrial fibrillation       | 190 2.9%     | 89 5.5%   | 101 2.1%       | <0.001|
| Peripheral vascular disease | 41 0.6%     | 15 0.9%   | 26 0.5%        | 0.12 |
| Heart failure             | 140 2.2%     | 42 2.6%   | 98 2.0%        | 0.19 |
| Stroke                    | 805 12.5%    | 280 17.2% | 525 10.9%      | <0.001|
| Diabetes                  | 436 6.8%     | 116 7.1%  | 320 6.7%       | 0.4  |
| Chronic kidney disease    | 88 1.4%      | 59 3.6%   | 29 0.6%        | <0.001|
| Liver disease             | 36 0.6%      | 16 1.0%   | 20 0.4%        | <0.05 |
| Depression                | 1781 27.6%   | 494 30.3% | 1287 26.8%     | <0.05 |
| Anxiety                   | 927 14.4%    | 200 12.3% | 727 15.1%      | <0.05 |
| Schizophrenia             | 92 1.4%      | 24 1.5%   | 68 1.4%        | 0.89 |
| Bipolar disorder          | 46 0.7%      | 18 1.1%   | 28 0.6%        | <0.05 |
| Substance abuse           | 779 12.1%    | 325 19.9% | 454 9.4%       | <0.001|
| Learning difficulties     | 218 3.4%     | 16 1.0%   | 189 3.9%       | <0.001|
| Total                     | 0 1912 29.6% | 457 28.0% | 1455 20.2%     |     |
| 1                         | 2182 33.8%   | 493 30.2% | 1689 35.1%     |     |
| 2                         | 1460 22.6%   | 379 23.2% | 1081 22.5%     | <0.001|
| 3                         | 638 9.9%     | 217 13.3% | 421 8.8%       |     |
| 4 +                       | 257 4.0%     | 85 5.2%   | 172 3.6%       |     |

Table 3
Persistence to ASM by order of therapy for new users.

| N | Persistent N (%) |
|---|------------------|
| Index drug | 1631 736 45.1% |
| First addition | 757 318 42.0% |
| Second addition | 297 132 44.4% |
| Third addition | 117 52 44.4% |
5. Existing user persistence

5.1. Overall persistence

Among the 4818 existing users, 2657 (55.1%) received no additional medications beyond those already prescribed at baseline, 1249 (25.9%) were prescribed one additional ASM during the study period, 516 (10.7%) were prescribed two, and 396 (8.2%) were prescribed three or more.

5.2. Prescribing in existing users and persistence to ASM

Patients who were persistent with additional medications ranged from 11.7% for retigabine to 54.0% for phenytoin. A summary of ASM prescribing and persistent rates at 365 days for the most commonly prescribed drugs is presented in Fig. 2. Only patients who were previously non-persistent during the lookback period are included in the persistence rates for index drugs, as the initiation dates for users who were persistent throughout the lookback period could not be confirmed.

6. Factors influencing persistence to ASM

The influence of clinical and demographic variables and the one-year persistence to index ASM in new and previously non-persistent existing users are summarised in Table 4.
6.1. Demographics

A number of demographic factors were associated with poor persistence. Age appeared to be an important determinant of persistence. Younger age groups (20–39 years) were significantly less likely to be persistent in comparison to those aged 60–69 years. In addition, socioeconomic disadvantage was a significant factor, with more affluent patients more likely to be persistent than those most deprived.

6.2. Comorbidity and polypharmacy

Perhaps counterintuitively, patients with more comorbidities demonstrated better persistence. This was particularly true for those with cardiac comorbidities and those who have previously had a stroke. In addition, those on four or more additional medications were more likely to persist with ASM treatment.

6.3. Additional clinical factors

Previously non-persistent users were less likely to be persistent at 365 days in comparison to new users. Use of newer ASMs was associated with higher rates of persistence, with patients prescribed second-generation ASMs more likely to be persistent than patients prescribed first-generation ASMs.

6.4. ASMs with potential neuropsychiatric adverse effects.

Amongst the 1046 patients prescribed an ASM with recognised potential for neuropsychiatric adverse effects, 315 (31%) had at least one mood-related psychiatric comorbidity at baseline. A separate, univariate analysis of these patients found no significant difference in persistence rates for ASMs with known neuropsychiatric adverse effects (OR 0.96, 95%CI 0.71–1.31).

7. Discussion

The aim of this study was to examine the rates of ASM persistence in a cohort of patients with epilepsy and investigate the associations between persistence and demographic and clinical features. Despite the increasing number of ASMs available to clinicians over the last 20 years more than 50% of new users of ASMs were not persistent at one year, much of which may not be recognised by the treating clinician.

We would argue that this study provides important information to help identify those patients more likely to demonstrate poor persistence and allow a different therapeutic approach and early intervention for those at highest risk. A small but significant proportion of new users were never persistent for a period of one year during the study period. Without medication, such patients are at higher risk of ongoing seizures and their attendant complications. Our assessment determined some demographic features associated with lower rates of persistence. In general, younger and most deprived adults were less likely to persist with ASMs. This highlights that additional service provision and/or clinical engagement may be required to meet the needs of these groups.

This study highlighted the burden of chronic poor health experienced by many PWE. More than 70% of those included in the cohort had multimorbidity. Overall, the frequency of physical comorbidities amongst this cohort was similar to those seen in a previous study of multimorbidity in patients with epilepsy in Scotland [9] but an higher frequency of psychiatric and psychological comorbidities was illustrated. Depression, anxiety, alcohol abuse and other psychoactive substance misuse were more common at baseline in this cohort in comparison to the larger, nationwide prevalence study. This may be due in part to the larger proportion of patients in this cohort from more deprived areas as social deprivation has previously been linked with increased prevalence of psychiatric comorbidity [11]. In this cohort, 52.6% of patients in this cohort were from the most deprived SIMD quintile compared with 14.6% in the previous studies – this is expected, as Glasgow has a generally high level of social deprivation, with over a third of the most deprived areas in the country being in Glasgow based on the 2012 SIMD [12]. The reported cumulative rate of depression, anxiety, and alcohol and psychoactive drug abuse highlighted the potential complexity faced by clinicians involved in the delivery of care to PWE, particularly within inner cities [10,13], and supports the call for regular screening of mental health as part of routine clinical practice, particularly within the out-patient setting.

In clinical practice, the choice of ASM may be influenced by fear of exacerbating existing underlying psychiatric conditions using particular ASMs. From the data presented, there was no supporting evidence to suggest that clinicians should wholly avoid prescribing ASMs associated with neuropsychiatric side effects in patients with mood disorders at
baseline compared to those without. This finding needs to be replicated in other larger cohort studies.

We found no association between comorbidity/multi-morbidity and low rates of persistence. There are several potential explanations to account for this. The first is that an individual’s persistence is not greatly influenced by number or type of comorbidities. An alternative explanation is that clinicians working within regional epilepsy clinics have the experience to consider the importance of comorbidity prior to recommending certain classes of ASM and are more cautious when prescribing certain ASM to those with additional comorbidity. The presence of multimorbidity was associated with increasing rates of persistence to ASM. Although this may appear to be counter intuitive, the same finding has been reported for other chronic conditions [14,15] and there are a number of potential explanations including the recognition that multimorbidity is often associated with the need for formal support and assistance with self-care, including the dispensing of medication.

The overall persistence to ASMs at one year among both new and existing users was around 40% for each therapy. This finding is relatively encouraging to both patients and health care professionals suggesting that each additional trial of therapy is not necessarily futile with many patients remaining on the additional ASM for more than one year. More clinical outcome measures such as admission rates or seizure freedom would be desirable and will be available as the dataset is developed further. Although the rate of persistence varied across different drugs, newer drugs including levetiracetam, lamotrigine, lacosamide and zonisamide had higher rates of persistence. This is particularly apparent in comparison to the oldest, first generation ASMs. As was demonstrated in previous publications, second generation ASMs have higher rates of persistence than first generation ASMs particularly among new users [7,16].

This study has a number of strengths. Within Scotland, the vast majority of health care for epilepsy patients is provided by the NHS thus the data are likely to be representative of the population of PWE. In addition, all encounters with NHS services can be accurately linked using their CHI number ensuring complete data capture [17]. All patients included were reviewed within a regional epilepsy center ensuring a relatively robust diagnosis and previous validation work within this cohort has demonstrated the search parameters show a high positive predictive value. The study is, however, not without limitations. Additional clinical factors such as epilepsy classification would have been desirable to provide a more complete phenotype. Persistence measurements here are all proxy measures derived from routinely collected data and may be subject to classification bias. It is also important to note that while pharmacy data indicate that a patient has been dispensed a medication they only give a maximum level of persistence (medicines might be collected but not ingested). Based on the available data, we were also unable to account for cases where non-persistence was a result of the patient ceasing taking their medications per their physician’s instructions after a period of seizure freedom. It is likely that this would only account for a limited proportion, if any, of the discontinuation of therapy reported here these results, as current NICE guidance recommends that discontinuation of ASM therapy be discussed with patients who have been seizure free for at least 2 years, and our main time point of interest was 1-year after initiation of each medication [2]. As described above, there are some differences in the demographic and clinical characteristics of this Glasgow cohort compared to a previous nationwide epilepsy cohort, and not all results will be generalisable to the whole population. Further research using a larger, nationwide cohort and incorporating information on medication adherence or more specific clinical features may help refine the findings from this study.

8. Conclusion

At present, these results highlight that demographic factors seem to be more important than individual comorbidities when predicting persistence. The risks emerging with inadequate control would suggest that additional input and support for those who are least likely to remain on ASM at one year should be considered with particular support aimed at younger patients from socially disadvantaged backgrounds. In an attempt address this issue within NHS GGC, routine dispensing data has been made available to clinicians within the Epilepsy out-patient clinic. This potentially allow HCP to identify those not engaging with the therapeutic process and to allow an enhanced level of care, support, and education. If successful, we hope to replicate this in the neighbouring health boards.

Supplementary material

**persistance_appendix.docx**

Declaration of Competing Interest

none

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2022.03.019.

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