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Characteristics and treatment outcomes of newly diagnosed epilepsy in older people: A 30-year longitudinal cohort study

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Keywords: antiseizure medication, efficacy, geriatric, new-onset epilepsy, tolerability

ABSTRACT

Objectives

To describe the clinical characteristics and evaluate the long term treatment outcomes in older people with newly diagnosed epilepsy over the past 30 years.

Methods

We included patients newly diagnosed with epilepsy and commenced on antiseizure medications (ASMs) at age of 65 years or older between July 1982 and October 2012 at the Western infirmary in Glasgow, Scotland. They were followed up till April 2016 or death. Seizure freedom was defined as no seizure for at least 1 year on unchanged medication at the last follow up.

Results

A total of 201 patients (median age 73 years, 59% male) were included. The median duration from initial seizure to starting treatment was eight months (interquartile range: 3.0 – 24.0); 42.2% (85/201) patients had more than five seizures before commencing treatment. Brain imaging showed potentially epileptogenic lesions in 19.7% (38/193) patients and other abnormalities in 56.5% (109/193). 78.6% patients (158/201) were seizure free at the last follow up, of whom 94.9% were taking monotherapy. Concomitant aspirin use (n=80) was associated with a lower probability of being seizure free (relative risk 0.82, 95% confidence interval 0.70 – 0.97; p=0.02). The use of second-generation ASMs as the initial monotherapy increased from 31.5% (23/73) before 2000 to 70.3% (90/128, p<0.001) from 2000 onwards. However, the seizure freedom rates (67.1% vs. 55.5%; p=0.35) and intolerable adverse effect rates (16.4% vs. 19.5%; p=0.45) did not show any significant difference.

Significance

There was often a long interval between seizure onset and the initiation of treatment in older people with new onset epilepsy, although the majority responded well to ASM treatment. Brain imaging showed a high rate of abnormalities. Despite the increased use of second-generation ASMs, treatment outcomes in later onset epilepsy have not improved over time. The possible effect of aspirin on treatment response warrants further investigation.

Keywords: antiseizure medication, efficacy, geriatric, new-onset epilepsy, tolerability

INTRODUCTION

The overall incidence of seizures is highest in the older age group, particularly in high income countries. [1] Older people with new onset epilepsy have poorer quality of life compared to those

with onset of epilepsy at a younger age. [2] In addition, epilepsy in old age has an adverse impact on rates of hospitalization and mortality compared to age matched general population, posing substantial financial burden on the individuals as well as the healthcare system. [3] With the continued ageing of the population, this burden is expected to rise further. [2]

New onset epilepsy in older people presents with unique set of challenges, both for the treating physicians and the patients. [4] Establishing the diagnosis of epilepsy in older people is not always straight forward as seizure semiology is often less reliable than in younger people, with more subtle clinical features, further masked by impaired cognitive profiles at baseline, leading to delay in treatment initiation. [5, 6] Furthermore, investigations are often unhelpful, as the interictal electroencephalography (EEG) may be less sensitive in older patients and the findings on brain imaging are often nonspecific. [4]

Selecting an appropriate antiseizure medication (ASM) in this age group can be challenging owing to the presence of multiple comorbidities impacting drug metabolism, and potential drug-drug interactions in the setting of polytherapy. [7] In addition, older patients are more sensitive to the adverse effects of ASMs, especially those affecting cognition and mood. [6] However, since the late 1980s, many new ASMs have become available with improved tolerability and safety profiles, raising hope that they might improve treatment outcomes in new onset epilepsy. [8] In this study, we report the real world experience of managing newly diagnosed epilepsy in older people over the past 30 years. We assessed the efficacy and tolerability of ASM treatments and examined whether the outcomes had changed over time.

METHODS

Study Population

Patients with newly diagnosed epilepsy seen at the Epilepsy Unit of Western infirmary in Glasgow, Scotland from 1 July 1982 to 31 October 2012 were included in the study. Patients were included in this analysis if they commenced treatment at or after 65 years of age. They formed part of the previous analyses on seizure outcome and treatment tolerability that included patients of all ages seen at the unit. [9, 10] Patients were followed up prospectively till 30 April 2016 or death. The study

was approved by the research ethics committee of Western Infirmary, Glasgow, who waived the requirement to obtain informed consent.

Treatment Approach

Details of initial clinical assessment, ASM treatment and follow up protocols have been described previously. [9, 11, 12] The choice of initial ASM was individualized and due consideration was given to patient characteristics such as comorbidities and concomitant drug use, type of epilepsy and tolerability profiles of each drug.

Patients were then evaluated at regular intervals, every two to six weeks for the first six months after commencing treatment, then every four months thereafter. The patients were instructed to maintain a seizure diary, noting the frequency of seizures. Drug dosages were adjusted on each visit, if indicated, depending upon efficacy and tolerability.

Monotherapy was the preferred treatment modality. If the single drug failed to provide seizure control or was not tolerated at a low dose, it was replaced by another agent. However, if initial monotherapy was tolerated well and provided meaningful seizure control but not complete remission, another suitable agent was added in combination. [13]

Definitions

Epilepsy was diagnosed after two or more unprovoked seizures more than 24 hours apart or a single unprovoked seizure with an increased risk for subsequent seizure, based on EEG or neuroimaging findings. [14] To classify semiology of seizures and sub-type of epilepsy, the latest International League Against Epilepsy (ILAE) classification schemes were used. [15, 16] The seizure classification was based on the history of seizure semiology, corroborated by a witnessed account, wherever possible, as well as interictal EEG abnormalities. Epilepsy syndrome was classified as either focal or generalized.

Seizure freedom was defined as no seizures for at least the previous 12 months on unchanged dosage at the time of last follow up. Similar to our previous study, intolerable adverse effects (AEs)

were defined as those stated as the main reason of discontinuation within 180 days of commencement of the ASM. [10]

The ASMs prescribed that were launched before 1980 were considered as first-generation ASMs (e.g. valproate, carbamazepine and phenytoin), and those introduced after that date were classified as second-generation ASMs (e.g. lamotrigine, gabapentin, oxcarbazepine, topiramate, levetiracetam and lacosamide). To assess the change in ASM prescribing practice and treatment outcomes of the initial ASM regimen over time, the study period was divided into two epochs according to the ASM start date, i.e. 1 July 1982 – 31 December 1999 and 1 January 2000 – 30 April 2016.

Potential risk factors for seizure outcomes were included in the seizure outcome analysis, [9] including seizure types (dichotomized to with or without tonic-clonic seizures), seizure duration (dichotomized to 5 years or less and more than 5 years), pretreatment seizure number (dichotomized to 5 seizures or less and more than 5 seizures), history of psychiatric disorders (dichotomized to yes and no), neuroimaging findings (categorized to normal, non-epileptogenic abnormal, and potentially epileptogenic), and other concomitant medications (dichotomized to no/other non-enzyme inducing medications and enzyme inducing medications). Concomitant medications that can potentially induce cytochrome P450 (CYP) enzymes that are essential for the metabolism of many medications were considered enzyme inducing medication.

Statistical Analysis

Fisher's exact test was used to assess the associations between categorical variables and Mann-Whitney test was applied for comparing continuous data. Generalized linear model for Poisson distribution with log link and robust error variance was used to assess the associations between potential risk factors and terminal seizure outcome with adjustments of age at treatment initiation and sex. Cox regression was used to estimate the difference in the probability of becoming seizure-free or having intolerable AE between the two epochs. Statistical significance level was set at $p<0.05$. Holm-Bonferroni method was applied to correct for multiple comparisons. All statistical tests were performed by using *Minitab* version 17 (Minitab Inc., State College, PA) and *Stata* version 16 (StataCorp, College Station, TX).

RESULTS

Patient Demographics and Clinical Characteristics

A total of 201 patients with new onset epilepsy, aged 65 years or above at treatment initiation, were included in the study. Demographic characteristics of the patients are shown in Table 1. Of the included patients, 115 (59%) were male. Median age at treatment initiation was 73 years (interquartile range [IQR]: 68 – 79; range 65 – 93). Epilepsy was classified as focal in all but one patient (99.5%). Median duration of follow up was seven and a half years (IQR: 4.2 – 13.6). The median time from the initial seizure to commencing treatment was eight months (IQR: 3.0 – 24.0), and was more than 12 months in over one third of patients. The number of seizures before treatment initiation was five or less in 116 (57.7%) patients, six to 19 in 32 (15.9%) and more than 20 in 53 (26.4%).

The majority of the patients (n=145, 72.1%) had other comorbid conditions besides epilepsy, most commonly hypertension, and cerebrovascular and cardiovascular diseases (Table S1). Sixty-seven percent (n=134) patients were taking at least one other concomitant drugs, ranging from 1 to 16 (median 3, IQR 2 – 4). Some of these drugs had potential interactions with ASMs via the CYP system (Table S2).

EEG and Neuroimaging Findings

EEG was performed in 107 patients with epileptiform abnormalities seen in 33 (30.8%) and was abnormal but did not reveal epileptiform abnormalities in 41 (38.3%). Neuroimaging was undertaken in 193 patients (34 had both magnetic resonance imaging [MRI] and computerized tomography [CT], 51 only had MRI and 108 only had CT). Overall, potentially epileptogenic abnormalities were revealed in 19.7% (38/193) patients, most commonly due to post-stroke gliosis/encephalomalacia (Table 2). A variety of non-epileptogenic abnormalities were seen in 56.5% (109/193) patients and no abnormality was found in 23.8% (46/193).

Treatment Outcomes

Seizure outcomes

All patients had at least 2 years of follow up after starting ASM therapy (median follow up duration 7.5 years, IQR 4.2 – 13.6). At the last follow up, the majority of the patients (n=184, 91.5%) were taking monotherapy, while the remaining (n=17, 8.5%) were on a combination of two ASMs. Lamotrigine was the most commonly prescribed monotherapy (n=76, 37.8%), followed by valproate (n=50, 24.8%), carbamazepine (n=29, 14.4%) and levetiracetam (n=13, 6.4%). No patient was taking more than two ASMs. Valproate was the most common concomitant ASM used in 70.6% (12/17) of the combined therapies and the most common combination was valproate and lamotrigine (n=6, Table S3). A total of 158 patients (78.6%) remained seizure free at the last follow up, of whom 75.9% (n=120) did so on their first ASM regimen (Table 3). The majority of the patients who achieved seizure freedom were taking monotherapy (n=149, 94.3%) and 5.7% (n=9) were on combined therapy. The doses of individual ASM regimens are shown in supplementary table (Table S3).

Factors associated with treatment outcome

In the multivariable analysis including potential risk factors associated with seizure outcomes, patients who were taking potential enzyme inducing concomitant medications at treatment initiation demonstrated significantly lower chance to achieve seizure freedom compared to those who were taking other non-enzyme inducing concomitant medications or not taking any concomitant medications at all (risk ratio [RR]=0.82; 95% confidence interval [CI]: 0.70 – 0.97; p=0.020; Table 4). Because aspirin was the only concomitant medication used by the patients that can potentially induce CYP enzymes, we performed further adjustment for history of cardio and/or cerebrovascular diseases that is correlated with aspirin use and an interaction term of the two variables. Although no significant effect was found in the interaction term (coefficient=0.00; 95% CI: -0.34 – 0.34; p>0.99), the predicted terminal seizure freedom rate was significantly lower in patients who had history of cardio and/or cerebrovascular diseases and taking aspirin (67.6%; 95% CI: 54.7 – 80.6%) than those patients who had no history of cardio and/or cerebrovascular diseases and not taking aspirin (88.9%; 95% CI: 82.0 – 95.8%; corrected-p=0.025). No other significant difference between the combinations of history of cardio and/or cerebrovascular diseases and aspirin use was found (Table S4).

Temporal Change in Antiseizure Medication Prescribing and Treatment Outcome

Of the 201 patients included in the analysis, 73 (36.3%) commenced their first ASM therapy in the first epoch (1 July 1982 – 31 December 1999) and 128 (63.7%) started treatment in the second (1 January 2000 – 30 April 2016). The number of patients used second-generation ASMs as the initial monotherapy increased from 31.5% (23/73) in the first epoch to 70.3% (90/128, $p<0.001$) in the second. However, the seizure freedom rates (first epoch: 49/73, 67.1% vs second epoch: 71/128, 55.5%; $p=0.35$; Figure 1A) and intolerable AE rates (12/73, 16.4% vs 25/128, 19.5%; $p=0.45$; Figure 1B) remained similar between the two epochs. Compared to the first epoch, multivariable analysis also found no significant differences in seizure freedom rate (adjusted hazard ratio [aHR]=0.88; 95% CI: 0.60 – 1.27; $p=0.48$) or intolerable AE rate (adjusted hazard ratio [aHR]=1.34; 95% confidence interval [CI]: 0.66 – 2.69; $p=0.42$) in the second epoch, after adjusted for pretreatment seizure duration, pretreatment seizure number, age and sex.

DISCUSSION

This longitudinal study investigated older people with new onset epilepsy over a 30-year period. An interval of more than six months between the initial seizure to commencement of ASM treatment was observed in the majority of patients. Neuroimaging revealed non-specific abnormalities in a large proportion. Nonetheless, once started on treatment, the response was good with nearly 80% patients ultimately achieving seizure freedom, mostly on their initial ASM. Patients taking aspirin for vascular diseases had poorer treatment outcome. Despite increased use of second generation ASMs the overall seizure freedom rate and tolerability had not improved in everyday practice over time.

Establishing the diagnosis of new onset epilepsy in the old age can be challenging. [5] The interval between seizure onset and treatment initiation in our study was considerably longer than that reported previously in a younger Australian cohort (n=220, median age 33 years, IQR 24 – 46 years), at more than six months (56% vs 21%) and >2 years (24% vs 14%), respectively. [17] In older people seizures may present with non-specific symptoms such as lapses in memory, delirium or syncope and dizziness. [18] Status epilepticus can present with prolonged confusion without clear convulsive activity. [5] Older people living alone are at particularly increased risk of experiencing

treatment delay. [17] Obtaining corroborative evidence and home-made videos can be helpful in establishing a correct and timely diagnosis. [6]

The EEG and brain imaging in older people reveal non-specific findings more often than in younger patients with epilepsy. [19] Yield of interictal EEG in older patients with new onset epilepsy is low (21– 37%), [20, 21] an observation confirmed in our study (30.8%). In comparison, 52% had epileptiform abnormalities on their first EEG in a cohort of 441 children and young adults with incident epilepsy. [22] Increasing the recording time and simultaneous video recording have been shown to increase the diagnostic yield of EEG in older populations. [20] The brain imaging in our study revealed abnormalities in a majority (76.2%, n=147) of patients. The diagnostic yield of epileptogenic abnormalities on imaging in localization related epilepsy ranges from 54 – 81% in younger cohorts [23, 24, 25] and 55.8 – 67.3% in older people with newly diagnosed epilepsy, [26] respectively. Overall, the low prevalence of epileptogenic lesions in our cohort could be under-estimation because a minority had an MRI of the brain (42.2%, n=85/201), including lower resolution scans done more than 20 years ago. However, the prevalence of other abnormalities was fairly high (56.5%, n=109). Whether these are merely reflective of old age and longstanding comorbidities or play a role in predisposing epileptogenesis remains to be determined.

Once the diagnosis of epilepsy in an older population has been made and appropriate treatment instituted, seizure freedom rate appears higher than in younger age groups, ranging from 83 to 92%. [5, 7, 27, 28] Ninety-four percent of the patients who achieved seizure freedom in our cohort did so on monotherapy, mostly on modest doses. It has been postulated that this favorable treatment response may be reflective of possibly lower epileptogenicity of the common underlying causative lesions encountered in this age group as well as lower likelihood of a genetic predisposition for recurrent seizures at play. [4]

Comorbidities were common in this population and two thirds of patients were taking at least one other concomitant medication, with a median of three. The heightened risk of drug-drug interaction due to polypharmacy in the older people with epilepsy has been well reported in studies of nursing home residents. [29] In our study, use of aspirin, specifically in patients who had cardio and/or cerebrovascular disease, was associated with lower predicted terminal seizure freedom rate. The

explanation for this is unclear. Aspirin was considered a potential CYP enzyme inducer in our analysis. A study in healthy volunteers found that short term (14 days) administration of low dose (50 mg/day) aspirin increased the *in vivo* activity of CYP2C19, [30] and a longer (4 weeks) exposure in rats seemed to induce the CYP enzymes more broadly. [31] However, strong clinical relevance of these effects is yet to be established. In addition, there is experimental evidence that aspirin induces the expression of P-glycoprotein, an efflux drug transporter. [32] Overexpression of P-glycoprotein at the blood-brain barrier is hypothesized to contribute to pharmacoresistance through reducing brain penetration of substrate ASMs. [33] An interaction between aspirin and underlying vascular diseases cannot be ruled out. Therefore, this finding of a potential effect of concomitant aspirin use on seizure outcome should be interpreted with caution and further investigation is needed.

It is generally considered that the first and second-generation ASMs have similar efficacy profiles, with the newer drugs offering improved tolerability and safety. [8, 34] Three randomized controlled trials have shown similar seizure control with lamotrigine (LTG) [35, 36] gabapentin (GBP), [35] levetiracetam (LEV) [37] and carbamazepine (CBZ) in older patients. One study noted trend towards higher seizure free rates with sustained release CBZ compared with LTG, however, the difference was not statistically significant. [38] In a retrospective study that compared tolerability of 10 ASMs in older patients, LTG was found to have the highest 12-month retention rate (78.6%) overall (without controlling for severity of epilepsy), which was significantly higher than that of phenytoin (PHT, 59.3%), GBP (59%), topiramate (TPM, 55.6%), CBZ (48.4%) and oxcarbazepine (OXC, 23.5%). In their analysis, LEV had the second highest retention rate (73%) and OXC fared the worst. [39] The similar efficacy between the first and second-generation ASMs, and variability in tolerability between the second-generation ASMs, may explain the observation that, despite the increased use of the latter, overall seizure outcome and tolerability of ASMs in our patients did not improve over time. However, the improved safety profile of non-enzyme inducing second-generation ASMs, particularly with regards to bone health (LTG and LEV) and development of vascular diseases as well as less chances of potential drug-drug interactions, offers an advantage while selecting ASM regimen in older individuals. [34, 40]

This study has limitations. The patients were seen at a single specialist center, hence the findings may not be generalizable to other populations. Treatments were not randomized but reflected how they were used in real world practice. The majority of the patients taking monotherapy (77%) were either on LTG, VPA or CBZ and therefore, the outcome data is more reflective of the use of these particular ASMs.

This study highlights the challenges in diagnosing and initiating treatment in older people with newly diagnosed epilepsy, who generally have a good treatment outcome. Despite similar efficacy to their older counterparts the second-generation ASMs, with generally fewer drug interactions and better long-term safety profile for some, [34] have enabled physicians to tailor therapy in older patients who have a high burden of comorbidities and concomitant medications. [8] Given the widespread use of aspirin in this age group for treatment of vascular diseases, the effect of concurrent aspirin use on ASM treatment outcome, if confirmed, could have important public health implication. Further research with larger sample size to verify this observation is warranted.

KEY POINTS

- A long interval between seizure onset and the initiation of treatment was commonly observed in older people with new onset epilepsy
- Brain imaging showed a high rate of abnormalities
- The majority of older people with newly diagnosed epilepsy responded well to ASM treatment
- Concomitant use of aspirin, specifically in patients with cardio and/or cerebrovascular disease, was associated with lower predicted terminal seizure freedom rate
- Despite the increased use of second-generation ASMs, terminal seizure freedom rate in older people with newly diagnosed epilepsy has not improved over time

DISCLOSURE OF CONFLICTS OF INTEREST

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ETHICAL PUBLICATION STATEMENT

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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FIGURE LEGENDS

Figure 1. Crude cumulative probability of (A) achieving seizure freedom and (B) withdrawal of the initial antiseizure medication as monotherapy due to intolerable adverse effects.

The navy blue and maroon lines represent the probabilities of (A) achieving seizure freedom and (B) withdrawal due to adverse effects of the initial antiseizure medication as monotherapy commenced in the two epochs (1 July 1982 – 31 December 1999 and 1 January 2000 – 30 April 2016). Shaded areas represent the 95% confidence intervals.

TABLES

Table 1. Characteristics of 201 older people with newly diagnosed epilepsy

Sex - n (%)		
Female	86	(42.8)
Male	115	(57.2)
Age at treatment initiation (years), median (IQR)	73	(68-79)
Duration of follow-up after treatment initiation (years), median (IQR)	7.5	(4.2-13.6)
Family history of epilepsy - n (%)	12	(6.0)
History of febrile convulsions - n (%)	3	(1.5)
History of birth trauma - n (%)	0	(0)
History of cerebral infection - n (%)	1	(0.5)
History of significant head trauma - n (%)	13	(6.5)
Cerebrovascular disease - n (%)	70	(34.8)
Number of patients taking concomitant drugs - n (%)	134	(66.7)
Taking an enzyme inducing drug (aspirin) – n (%)	80	(39.8)
Number of concomitant drugs, median (IQR)	3	(2-4)
Number of the pre-treatment seizures - n (%)		
1	24	(11.9)
2	39	(19.4)
3-5	53	(26.4)
6-10	20	(10.0)
11-20	12	(6.0)
>20	53	(26.4)
Duration of the pre-treatment seizures (months) - n (%)		
<2	37	(18.4)
2-6	50	(24.9)
7-12	38	(18.9)
13-24	27	(13.4)
25- 60	26	(12.9)
>60	23	(11.4)

Seizure classification - n (%)		
Focal seizures only	78	(38.8)
Focal to bilateral generalised tonic-clonic seizures only	71	(35.3)
Both focal and focal to bilateral tonic-clonic seizures	51	(25.4)
Absence with bilateral tonic-clonic seizures	1	(0.5)
Epilepsy classification (based on seizure type) - n (%)		
Generalised	1	(0.5)
Focal	200	(99.5)

IQR, interquartile range.

Table 2. Neuroimaging findings in elders with epilepsy in Glasgow, UK

Neuroimaging Findings *	**MRI (n=85) n (%)**		**CT Only (n=108) n (%)**		**Total (N=193) n (%)**	
Potentially epileptogenic abnormalities	**13**	**(15.3)**	**25**	**(23.1)**	**38**	**(19.7)**
Post-stroke gliosis/encephalomalacia	6	(46.2)	20	(80.0)	26	(68.4)
Focal atrophic changes	3	(23.1)	1	(4.0)	4	(10.5)
Meningioma	1	(7.7)	3	(12.0)	4	(10.5)
Arteriovenous malformation	0	(0)	2	(8.0)	2	(5.3)
Ependymal cyst	1	(7.7)	0	(0)	1	(2.6)
Mesial temporal sclerosis	1	(7.7)	0	(0)	1	(2.6)
Post-traumatic gliosis/encephalomalacia	1	(7.7)	0	(0)	1	(2.6)
Non-epileptogenic abnormalities	**61**	**(71.8)**	**48**	**(44.4)**	**109**	**(56.5)**
Cerebral atrophy	27	(44.3)	35	(72.9)	62	(56.9)
Small vessel ischaemic change	39	(63.9)	18	(37.5)	57	(52.3)
Nonspecific small lesions	7	(11.5)	8	(16.7)	15	(13.8)
Cerebellar Atrophy	3	(4.9)	9	(18.8)	12	(11.0)

Nonspecific white matter/T2 weighted hyperintensity	4	(6.6)	0	(0)	4	(3.7)
Ventriculomegaly	2	(3.3)	1	(2.1)	3	(2.8)
Cerebral artery aneurysm	2	(3.3)	0	(0)	2	(1.8)
Asymmetry of ventricles	0	(0)	1	(2.1)	1	(0.9)
Hippocampal grey matter volume increase	1	(1.6)	0	(0)	1	(0.9)
Nonspecific small cystic lesions	1	(1.6)	0	(0)	1	(0.9)
No abnormality detected	**11**	**(12.9)**	**35**	**(32.4)**	**46**	**(23.8)**

* Some patients had more than one abnormality.

Table 3. One-year seizure freedom rates with successive antiseizure medication regimens

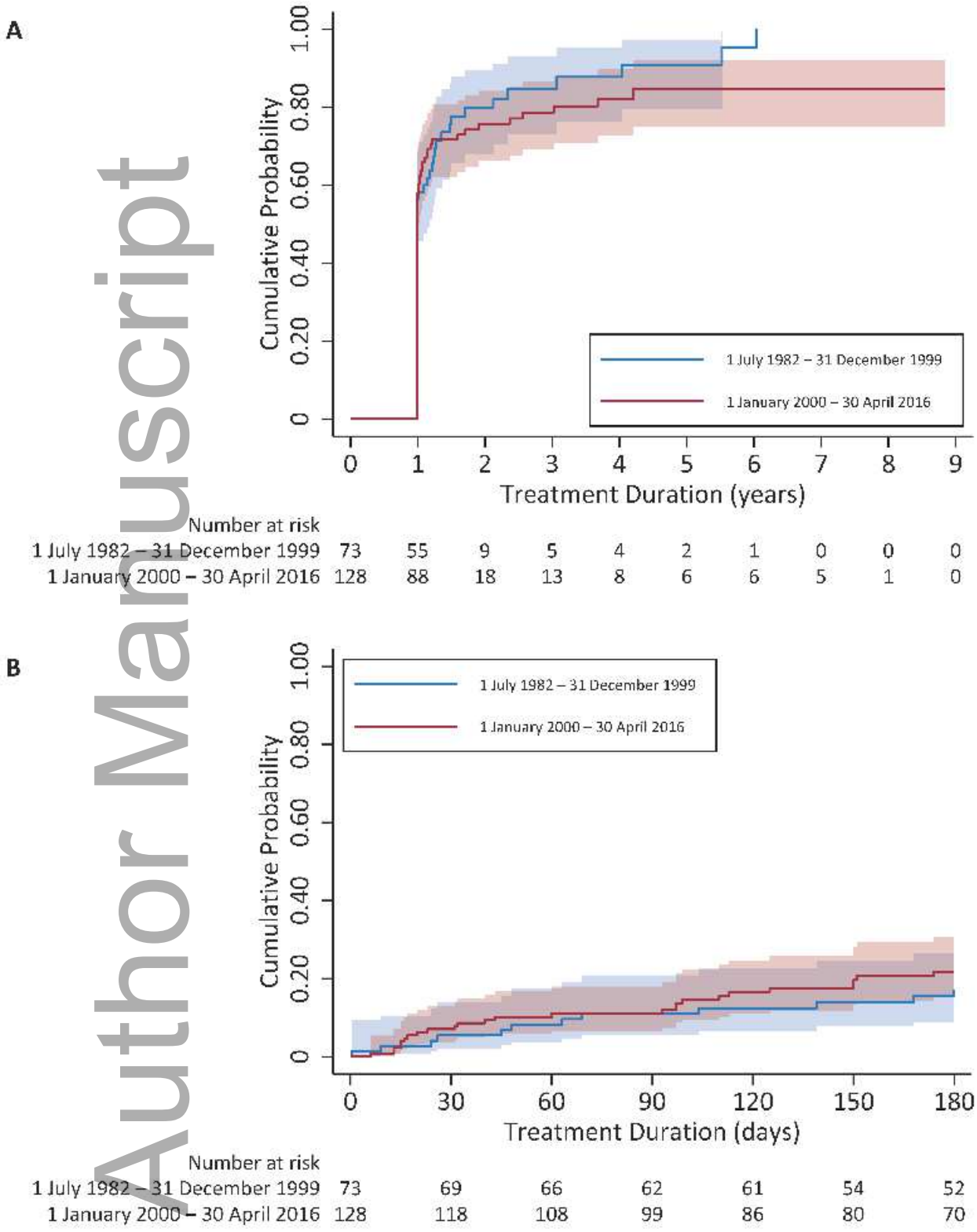
ASM regimens	Number of patients trying the ASM regimen	Patients achieving seizure freedom			
		n	% of patients who took the ASM regimen	% of 158 patients achieving seizure freedom	% of total 201 patients
First	201	120	59.7	75.9	59.7
Second	55	28	50.9	17.7	13.9
Third	15	9	60.0	5.7	4.5
Fourth	3	1	33.3	0.6	0.5
Total		**158**		**100**	**78.6**

ASM, antiseizure medication.

Table 4. Multivariable generalised linear model for terminal seizure freedom

	Seizure freedom - n (%)	RR	(95% CI)	p-value
Had TCS vs no-TCS	97/123 (78.9) vs 61/78 (78.2)	0.95	(0.82-1.11)	0.53
Seizure duration (>5 yrs vs ≤5 yrs)	19/23 (82.6) vs 139/178 (78.1)	1.00	(0.80-1.24)	0.97
Number of pretreatment seizure (>5 vs ≤5)	65/85 (76.5) vs 93/116 (80.2)	0.94	(0.80-1.10)	0.44
History of psychiatric disorders	15/22 (68.2) vs 143/179 (79.9)	0.98	(0.73-1.33)	0.91
Neuroimaging findings - Reference Normal	41/46 (89.1)			
Abnormal	85/109 (78.0)	0.88	(0.76-1.02)	0.081
Epileptogenic	28/38 (73.7)	0.83	(0.67-1.03)	0.086
Taking concomitant medications - enzyme inducing vs. no concomitant/others	55/80 (68.8) vs 103/121 (85.1)	0.82	(0.70-0.97)	0.020
Age at treatment initiation		1.01	(0.99-1.02)	0.27
Sex - Male vs Female	95/115 (82.6) vs 63/86 (73.3)	1.11	(0.94-1.29)	0.21

CI, confidence interval; RR, risk ratio; TCS, tonic-clonic seizure.



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