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Treatment initiation decisions in newly diagnosed epilepsy – A longitudinal cohort study

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Keywords: Early-seizures, management, patient-preference

SUMMARY

Objective: To examine the factors and reasons influencing treatment initiation decisions in newly-diagnosed epilepsy patients.

Methods: We assessed anti-seizure medication initiation decisions in adults with newly-diagnosed epilepsy seen at first seizure clinics in Western Australia between 1999 and 2016 and followed to 2018.

Results: Of 610 patients (median age 40 years, 61.0% male), 426 (69.8%) were diagnosed after ≥2 seizures and 184 (30.2%) after a single seizure with risk factors for recurrence. Treatment was commenced in 427 (70.0%) patients at diagnosis, 112 (18.4%) during follow-up, mostly after further seizures, while 71 (11.6%) remained untreated at last follow-up. Elders (≥65 years, odds ratio [OR]=3.06, 95% confidence interval [CI]: 1.62–5.80), more seizures (OR=3.48, 95% CI: 2.03–5.96) and epileptogenic lesions on neuroimaging (OR=2.15, 95% CI: 1.26–3.68) had a higher likelihood of treatment at diagnosis. Patients with less than one seizure per year within the preceding year (OR=0.40, 95% CI: 0.21-0.73) and of higher socio-economic status (OR=0.985, 95% CI: 0.977–0.994) were less likely to be treated. For 93 (15.2%) patients, treatment was not recommended at diagnosis, most commonly because only a single seizure had occurred. 90 (14.8%) patients declined recommended treatment, mostly because they were unconvinced of the need for treatment or the diagnosis.

Significance: 30% of adults with newly-diagnosed epilepsy were not immediately treated. Treatment initiation in this real-world cohort was influenced by age, number of seizures prior to diagnosis, imaging findings, patient preferences and socio-economic status.

Keywords: Early-seizures, management, patient-preference

KEY POINT BOX

• Nearly one-third of adult patients with newly diagnosed epilepsy were not treated or had delayed treatment in specialist clinic practice.

• Elders, more seizures and epileptogenic lesions on neuroimaging were associated with higher likelihood of treatment at diagnosis.

• No seizure within the preceding year and higher socio-economic status were associated with lower likelihood of treatment at diagnosis.

• Having had only a single seizure was the most common reason for neurologists not recommending anti-seizure medication therapy at diagnosis.

• Being unconvinced of the need for treatment or of the diagnosis were the most common reasons for patients declining neurologist-recommended treatment.

INTRODUCTION

Epilepsy affects an estimated 68 million people worldwide with an incidence of 45 – 82 per 100,000 per year [1]. Minimising the consequences of recurrent seizures is an important public health priority. Anti-seizure medications (ASMs) can render up to two-thirds of patients seizure-free[2]. Untreated epilepsy has long been highlighted as a public health concern in lower-income countries, where up to 90% or more of patients do not receive regular ASM therapy[3, 4]. This phenomenon is generally attributed to socioeconomic factors, including lack of access to trained clinicians and cost of ASM therapy, superstitious and cultural beliefs, and the predominance of traditional treatments[4, 5].

To what extent people with epilepsy in high-income countries are not treated has not been well studied, although the reported proportion has generally been considered small[3]. In the

National Health Interview Surveys conducted in 2013 and 2015 in the United States, 10% of adults self-reported to have active epilepsy were not taking anti-seizure medications at the time of the surveys[6]. However, a recent assessment of 1,942 French patients with newly diagnosed epilepsy reported approximately 28% of patients from neurologist survey were not treated at diagnosis[7]. Additionally, two assessments of US insurance claim databases identified over 50,000 patients with incident epilepsy between 2010 and 2015 and examined the treatment rate in newly diagnosed epilepsy. Only 48.6% were treated within six months after a coded diagnosis of epilepsy, and 63.3% by three years after diagnosis[8, 9]. These studies, based on self-report or hospital discharge coding, are limited by diagnostic uncertainty, short follow-up duration for most patients and the inability to assess the reasons for no treatment.

Limited evidence exists to guide treatment decisions. The MESS Trial conducted between 1993 and 2000 in the United Kingdom examined patients aged at least one month with one or more unprovoked seizures, in whom both the clinician and the patient were uncertain whether to commence treatment. Patients were randomised to immediate treatment or delaying treatment until the clinician and patient agreed that treatment was necessary, with no long-term benefits of immediate treatment[10]. However, the reasons for the "uncertainty", and number of seizures leading to treatment initiation in the delayed group, were not reported[11].

This study aimed to examine the rate of non-treatment in patients with newly diagnosed epilepsy in a high-income country, and the factors and reasons influencing treatment decisions at the time of diagnosis and during follow-up.

METHODS

Setting

Eligible patients of ≥15 years were identified from the First Seizure Clinics at two tertiary adult hospitals in Western Australia. The clinics are led by the same group of neurologists within a single specialised epilepsy service and receive referrals of adults with suspected seizures from hospital emergency departments and primary care physicians across the state[12]. The Australian tax-funded healthcare system provides universal coverage for all public hospital admissions, outpatient attendances, investigations and treatment. The Pharmaceutical Benefits Scheme subsidizes all common ASMs available in Australia.

The study was approved by the Royal Perth Hospital Human Research Ethics Committee (Reference number: EC 2009/054) and registered with the Monash University Human Research Ethics Committee (project number: 12131).

Patients

Patients with newly diagnosed epilepsy at the clinics between 1st May 1999 and 31st May 2016 were eligible for inclusion. We excluded patients who had a previous diagnosis of epilepsy, or had ever been treated with ASMs either for seizure prevention or any other indication.

Definitions

Patients were considered to have epilepsy based on the diagnosis of the treating neurologist. In principle, the diagnosis was made after two or more unprovoked seizures occurring more than a day apart, or a single unprovoked seizure in the presence of risk factors or investigations suggesting a high risk of recurrence including an epileptiform abnormality on EEG, an epileptogenic lesion on neuroimaging or remote symptomatic aetiology. This approach is consistent with definitions later published by the International League Against Epilepsy (ILAE) in 2005[13] and 2014[14], that have been subsequently validated for patients with a single seizure at diagnosis[15].

Patients were classified as untreated if they had not been commenced on ASM therapy, regardless of whether treatment was recommended or declined. The presence or absence of neuroimaging lesions considered to be epileptogenic[16, 17], and epileptiform abnormalities on EEG[18] were documented. Investigations ordered prior to diagnosis were individualised, with patients having one or more routine, sleep-deprived or prolonged EEG, as well as either or both of computed tomography or magnetic resonance imaging scanning as clinically indicated. Epilepsy type (focal, generalized or unclassified) was defined on the basis of the seizure semiology, EEG and neuroimaging results, and other medical history as appropriate. The number of seizures included the index event that led to the referral and included all types of countable seizures. Seizures occurring in the setting of potential precipitants related to lifestyle/external factors (e.g. sleep deprivation, stress) were regarded as unprovoked unless the factors met the criteria for acute symptomatic seizures according to ILAE guidelines (e.g. acute stroke, severe metabolic derangement)[19]. Socio-economic status was measured by the continuous 2011 Index of Relative Socio-economic Advantage and Disadvantage scale,

where patients' socio-economic status was represented by that of the area they resided in[20]. Ethnicity was based on self-reported information.

Data sources and extraction

Data was extracted from complementary sources in a two-step process. First, we reviewed the First Seizure Database, prospectively maintained by the Western Australian Adult Epilepsy Service[12, 21]. This database contains extensive demographic and clinical data of consecutive patients seen at the First Seizure Clinics, including age, dates of initial and subsequent seizures, and results of the initial and subsequent EEGs and neuroimaging. This prospectively obtained database was used to identify patients potentially eligible for inclusion.

In the second step, the medical record of each potential patient was retrospectively reviewed, including correspondence with the patient's primary care physician and other specialists, hospital discharge summaries, and investigation reports. Information in the First Seizure Database and the patient's medical record was cross-checked to ensure accuracy. Patients who failed to attend clinic follow-up were contacted by telephone to ascertain if they were subsequently initiated on ASM therapy. Data for all patients was entered into a pre-designed proforma in REDCap[22], an online survey and database management application.

Factors potentially affecting the treatment decision were consolidated to the point at which epilepsy was diagnosed by the treating neurologist. These included demographic factors, epilepsy-related factors such as epilepsy type[23], presentation with a cluster of seizures (two or more seizures with recovery between within 24 hours), status epilepticus, occurrence of tonic-clonic seizures prior to diagnosis, number of separate seizure events and the results of the investigations performed. Patients were also grouped into low, medium, and high seizure recurrence risk categories as per findings from the MESS Trial, which stratified patients based on the number of seizures prior to presentation with additional risk incurred by abnormal EEG, as well as any of neurological disorder or deficit, learning disability or developmental delay (detailed in Methods S1). These groups respectively correspond with a 19% (low), 35% (medium) and 59% (high) probability of seizure recurrence within one year in patients with a first seizure or newly diagnosed epilepsy who were not initially treated[24]. These risk classifications were compared against treatment recommendation and treatment initiation in our cohort. For patients not treated at diagnosis, reasons for not recommending or

for patients declining therapy, number of seizures experienced and new investigation results, and reason for treatment initiation during follow-up were recorded.

The medical records were reviewed by two investigators (S.S. and M.R.). To assess inter-observer variability, the records of a random sample of 80 (13.1%) patients were reviewed by both investigators. They were assessed with regard to the determination of whether the patient was diagnosed with epilepsy, status of ASM treatment, and reasons for not starting treatment. The comparisons showed very strong interobserver agreement (coefficient kappa >0.90). Discrepancies were adjudicated by a senior epileptologist (P.K.).

Statistical analysis

Continuous variables were reported as medians and interquartile range (IQR) due to non-normal distribution. All categorical and continuous independent variables were assessed against whether treatment was initiated at diagnosis using a penalised-likelihood logistic regression, as quasi-complete separation occurred in the data. Variables with a p-value<0.2 in univariable analysis were included in the multivariable model. Assessment comparing patients who had one EEG to those who had two or more prior to diagnosis, and between patients with epileptiform EEG abnormalities or not, was performed using Fisher's exact test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. Variables for this assessment were those included in multivariable analysis for treatment decision, and p-values were corrected using the Holm-Bonferroni (HB) method. Unless stated otherwise, significance level of p=0.05 was used. All statistical tests were performed by using *Stata 14* (StataCorp, College Station, TX), with user-written package 'firthlogit'[25].

RESULTS

Patient characteristics

Six hundred and ten patients were newly diagnosed to have epilepsy by the treating neurologists and included as the study cohort. All of these patients also satisfy the later ILAE diagnostic criteria for epilepsy published in 2014[14]. Their characteristics are described in Table 1. The median follow-up after diagnosis was 5.0 years (IQR 2.5 – 8.2).

The majority (69.8%) of patients were diagnosed with epilepsy after the occurrence of two or more unprovoked seizures. Among the 184 patients diagnosed after only one documented seizure, their epilepsy diagnosis was supported by the presence of one or more of epileptogenic neuroimaging findings in 124 (67.4%), epileptiform EEG abnormalities in 53

(28.8%), or remote risk factors such as developmental disability or suspected but not definite prior seizures in 35 (19.0%). Based on the MESS Trial classification, 18 (3.0%) patients were classified as low risk for seizure recurrence (diagnosed by their neurologist due to one seizure and suspected but not definite prior events), 291 (47.7%) medium risk and 301 (49.3%) high risk.

Of patients assessed with any EEG, those assessed with multiple recordings prior to diagnosis were more likely to have a greater number of seizures prior to diagnosis (HB-corrected p=0.008), and more likely to be of unknown/unclassified epilepsy type (HB-corrected p=0.047). These patients were also less likely to have had epileptiform abnormalities identified on the initial EEG (HB-corrected p<0.001), and less likely to have an epileptogenic lesion found on neuroimaging prior to diagnosis (HB-corrected p<0.001), Table S1).

Treatment initiation at diagnosis

Figure 1 shows the treatment course of the 610 patients included for analysis at diagnosis and during follow-up. At diagnosis, ASM treatment was recommended in 517 patients, 427 of whom accepted the recommendation and 90 declined, while ASM treatment was not recommended in 93. Thus 427 patients (70.0%) commenced ASM treatment at the time of diagnosis and 183 (30.0%, of whom 72 [39.3%] had a single seizure at diagnosis) did not.

Of the 426 patients with two or more unprovoked seizures, who might be regarded as having a more "classic" diagnosis of epilepsy, 370 (86.9%) had ASM therapy recommended, of whom 55 (14.9% of 370) declined (overall 26.1% [111/426] untreated). Of the 184 patients with a single seizure who met the new ILAE diagnostic criteria for epilepsy, 147 (79.9%) had ASM recommended, of whom 35 (24.0% of 147) declined (overall 39.1% [72/184] untreated).

Univariable penalised logistic regression analysis demonstrated that older age, having a higher number of seizures before diagnosis, presence of epileptogenic neuroimaging abnormalities, focal rather than generalised epilepsy, having experienced clusters of seizures, and having seizures unspecified to be while awake or asleep were associated with a higher likelihood of being treated at diagnosis (Table S2). Having fewer than one seizure per year since the first seizure prior to diagnosis, epileptiform EEG changes, unclassified epilepsy

type, higher socio-economic status and the presence of lifestyle/external factors were associated with a lower likelihood of being treated at diagnosis.

Based on the MESS Trial classification, patients defined as having a high risk of seizure recurrence (Supplementary Methods) were associated with a higher likelihood of commencing therapy (OR=3.64, 95% CI: 1.42-9.33) than low risk patients, but the difference was not significant for those of medium risk (OR=2.46, 95% CI: 0.97-6.29).

Multivariable analysis is reported in Table 2. Increased age was associated with higher likelihood of treatment initiation at diagnosis (patients ≥65 years of age compared to those of 18 up to 65 years: OR=3.06, 95% CI: 1.62-5.80; patients <18 years of age compared to those of 18 up to 65 years: OR=0.45, 95% CI: 0.22-0.94). Those with epileptogenic neuroimaging abnormalities at the time of diagnosis were more than twice as likely to begin treatment at diagnosis (OR=2.15 95% CI: 1.26-3.68), but epileptiform abnormalities on initial or subsequent EEG did not influence the decision to start treatment (OR=0.79, 95% CI: 0.47-1.33). Patients with more than one seizure before diagnosis were over three times more likely to start therapy at diagnosis than patients with one seizure (OR=3.48, 95% CI: 2.03-5.96), and having less than one seizure per year after the first seizure prior to diagnosis was associated with a lower likelihood of starting therapy (OR=0.40, 95% CI: 0.21-0.73). Patients with a cluster of seizures prior to diagnosis were more likely to be treated (OR=2.57, 95% CI: 1.42-4.66). Having lifestyle/external factors associated with seizures also correlated with a lower likelihood of commencing therapy (OR=0.67, 95% CI: 0.46-0.97), as was higher socio-economic status, with each point of increase in percentile score associated with the patient being 1% less likely to start therapy (OR=0.985, 95% CI: 0.98-0.994).

A separate multivariable analysis including only patients with two or more unprovoked seizures (a “classic” diagnosis of epilepsy) at diagnosis yielded similar findings (Table S3). However, in this group, the number of seizures prior to diagnosis did not alter the likelihood of treatment initiation. Another separate analysis of patients aged from 18 to 55 was performed to assess for the impact of reproductive potential, and gender was not associated with an altered likelihood of treatment initiation (OR=1.55, 95% CI: 0.98-2.48). All other factors significant in this specific age group were similar to the larger cohort.

Analyses in patients with and without epileptiform EEG findings have found patients with epileptiform abnormalities on initial or subsequent EEG were likely to be younger (HB-corrected p=0.003), not have concurrent epileptogenic lesions identified on neuroimaging (HB-corrected p=0.01) and be of generalised rather than focal or unknown/unclassified epilepsy type (HB-corrected p<0.001, Table S4). Additionally, in patients without epileptogenic lesions and with a single seizure at diagnosis (n=60), all 28 patients without epileptiform EEG had other risk factors (learning/developmental disability or history of suspected but not confirmed seizures) and only 9.4% (3/32) of those with epileptiform EEG had other risk factors. These other risk factors were associated with increased likelihood of treatment initiation (OR=4.36, 95% CI: 1.43-13.3). Finally, although 65.6% (21/32) of patients diagnosed only with a single seizure and epileptiform EEG were offered treatment at diagnosis, only 33.3% (7/21) accepted this recommendation. In comparison, 86.4% (89/103, p=0.017) patients with only epileptogenic lesions and a single seizure were offered treatment, and 85.4% (76/89, p<0.001) accepted. 82.8% (192/232, p=0.030) patients diagnosed with multiple seizures alone were offered treatment and 82.8% (159/192, p<0.001) accepted.

Per patient reasons for not commencing therapy at diagnosis

Of the 183 patients who were not commenced on treatment at diagnosis, ASM therapy was not recommended by their neurologists in 93, and 90 declined ASM therapy despite this being recommended. Of 93 patients in whom therapy was not recommended by their neurologist, 81 (87.1%) had a single reason, 11 (11.8%) had two reasons, and one (1.1%) had three reasons. The most common reasons (table 3A) were: only a single seizure had occurred (n=25), the neurologist opted to await further results (n=24), and the presence of avoidable lifestyle/external factors (n=19).

Of the 90 patients who declined therapy at the time of diagnosis, 82 (91.1%) had a single reason, and eight (8.9%) had two reasons. The most common reasons (table 3B) were that patients: were unconvinced of the necessity for treatment (n=40), were unconvinced of the diagnosis (n=16) and preferred to avoid possible precipitating lifestyle/external factors (n=12).

Delayed treatment initiation after diagnosis

During subsequent follow-up, 61.2% (112/183) of the initially untreated patients were started on ASMs. Among them, 31 commenced treatment outside clinic visits and the reason for

ASM initiation and the number of seizures they experienced before treatment, could not be ascertained. The remaining 81 patients experienced a median delay of 112 days (IQR 35 – 329) from diagnosis to treatment initiation. The most common reason for commencing treatment was having further seizures (n=73 [90%]). 35 had one further seizure, 14 had two, 11 had three, three had four, ten had five or more, and an undetermined number in two patients.

Other reasons for commencing ASM were new epileptiform EEG findings (five patients), having other potential causes for seizure ruled out (four patients) and wanting to drive (four patients). One patient each commenced therapy due to employer pressure, injury or fear of injury, and being post-lesionectomy for an epileptogenic lesion. New epileptiform EEG findings also were also identified in seven additional patients and new MRI findings in four patients, but without leading to a decision to initiate therapy.

DISCUSSION

We observed in a well-resourced, specialist clinic setting that 30% of patients were not started on ASM treatment at diagnosis, and approximately one in nine remained untreated at the end of follow-up. Most previous studies in high-income countries have generally reported untreated epilepsy rates of less than 10%[3, 6]. However, these cross-sectional surveys were unable to capture the details of changes in treatment decisions over time with no data on rate of treatment at diagnosis. Using insurance claims databases, recent studies in the United States found that the untreated proportion of patients recently diagnosed with epilepsy was in excess of 50%[8, 9]. Similarly, our study of patients at the time of diagnosis suggests the rate might be higher than previously appreciated.

Several factors appeared to be influential in the decision to commence ASM treatment at diagnosis. Patients were more likely to be treated if they were older, perhaps because older patients can be accustomed to and may accept taking regular medications. While the occurrence of a cluster of seizures (multiple within 24 hours) in new-onset seizures is not risk factor for recurrence[12], it was associated with an increased likelihood of treatment initiation at diagnosis, in keeping with the requirement for ASM initiation in the emergency department or neurology ward due to the repeated events. Additionally, having seizures associated with lifestyle/external factors such as sleep deprivation was associated with a lower likelihood of treatment, reflected by the preference of some patients and/or neurologists to reduce the risk of further seizures by modifying lifestyle/external factors rather than starting ASM.

Epileptiform EEG changes played a lesser role than neuroimaging abnormalities in influencing treatment commencement and remained less influential than other risk factors in those with normal imaging and a single seizure. This observation might reflect inherent differences in weighting ascribed by neurologists to different investigations in the treatment decision process[26]. While EEG has consistently been associated with a higher risk of recurrence after a first seizure [27], its role in our cohort might have been to clarify electroclinical diagnosis when other data was non-contributory and was not a predictor of treatment in our study. In our cohort where all patients were diagnosed with epilepsy, a higher proportion of patients had epileptogenic lesions (over 40%) identified on neuroimaging compared to similar cohorts[10, 16, 17]. These played a significant role in treatment initiation, while patients with epileptiform EEG findings were less likely to also have an epileptogenic lesion. Even in patients diagnosed after a single seizure without epileptogenic lesions, other underlying risk factors for seizure recurrence such as learning/developmental disability or a history of suspected seizures were more influential. Further, not all patients had EEG prior to diagnosis. In patients diagnosed after multiple seizures or a single seizure with an epileptogenic lesion identified on neuroimaging or other risk factors for whom there was clear impetus to treat, EEG might not have been ordered or was only performed after diagnosis to inform subsequent management. Finally, the patient ultimately accepted or declined the recommendation to commence treatment. Most patients with epileptiform EEG findings were offered therapy, but a smaller number accepted compared to those diagnosed with neuroimaging lesions or recurrence seizures, suggesting that patients themselves may be less influenced by EEG findings than seizures they have experienced or often symptomatic epileptogenic lesions.

Socio-economic status was higher among patients not commencing treatment at diagnosis. A previous small study performed in India found that manual laborers involved in lower-income risky jobs (such as construction work) were more likely to opt for ASM treatment[28]. It is possible that people of higher socio-economic status are more able to adjust their occupations to mitigate the potential harm from untreated recurrent seizures.

Analysis performed at the individual patient level showed both similarities and differences in neurologist and patient reasons for not commencing treatment, reflecting different risk-benefit considerations in the decision-making process. Having had only a single seizure event

was the most common reason for neurologists not recommending ASM therapy at diagnosis. This decision is supported by previous studies of patients with single seizure or "early" epilepsy, notably the MESS and FIRST trial groups, which showed that early treatment did not affect long-term seizure outcome compared to delayed treatment[10, 29, 30]. The second most common reason for neurologists not recommending ASM therapy at diagnosis was that further investigation results were required to characterise the epilepsy, which can enhance diagnostic certainty and influence ASM choice[31]. These are clearly reasoned, literature-supported decisions and do not necessarily represent a deficiency in management, although there is a paucity of evidence regarding the outcomes of deferred treatment in patients newly diagnosed with epilepsy, particularly in those with a single seizure who meet the new diagnostic criteria for epilepsy.

The majority (61.2%) of the initially untreated patients started ASM treatment during follow-up, overwhelmingly because they had had further seizures. This suggests that in deciding to commence therapy, both neurologists and patients often place greater emphasis on actual seizure recurrence rather than predictions of risk of seizure recurrence. Additionally, although a previous assessment of quality of life after immediate or deferred treatment following a single seizure described a disadvantage of deferred therapy in terms of delay in regaining a driver's license[32], this influenced treatment decisions in only a small number of patients. Our findings highlight the ongoing importance of individualised patient preferences in treatment decisions.

Limitations

Medical records were retrospectively reviewed to determine the treatment status and the reasons for the treatment decision, but these might not have been explicitly or fully documented. Patients were also seen in dedicated tertiary hospital-based specialist clinics which may be biased towards those with more severe epilepsy. If so, it is possible that the rate of untreated epilepsy is higher in the community[6]. Finally, our study included mainly adults (youngest age 15 years), hence the findings may not be extrapolated to children.

CONCLUSIONS

Despite accessibility to specialist care and ASMs, 30% of adult patients with newly diagnosed epilepsy were not treated or experienced delayed treatment in clinical practice. In this real-world cohort a diagnosis of epilepsy did not carry with it an automatic and

immediate decision to treat, but a nuanced process of individualised risk assessment occurs that ultimately is influenced by patient preferences. To more accurately understand the decision to start or withhold treatment, prospective and independent assessment of both the clinician's and patient's perspectives are needed.

ETHICS 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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REFERENCES

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: A systematic review and meta-analysis. Neurology. 2011;77:1005-12.

2. Kwan P, Brodie MJ. Early Identification of Refractory Epilepsy. N Eng J Med. 2000;342:314-9.

3. Meyer AC, Dua T, Ma J, Saxena S, Birbeck G. Global disparities in the epilepsy treatment gap: a systematic review. Bull World Health Organ. 2010;88:260-6.

4. Meyer AC, Dua T, Boscardin WJ, Escarce JJ, Saxena S, Birbeck GL. Critical determinants of the epilepsy treatment gap: a cross-national analysis in resource-limited settings. Epilepsia. 2012;53:2178-85.

5. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. Epilepsia. 2008;49:1491-503.

6. Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active Epilepsy and Seizure Control in Adults - United States, 2013 and 2015. MMWR Morb Mortal Wkly Rep. 2018;67:437-42.

7. Jallon P, Loiseau P, Loiseau J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Epilepsia 2001;42:464-475

8. Faught E, Helmers S, Thurman D, Kim H, Kalilani L. Patient characteristics and treatment patterns in patients with newly diagnosed epilepsy: A US database analysis. Epilepsy Behav. 2018;85:37-44.

9. Kalilani L, Faught E, Kim H, Burudpakdee C, Seetasith A, Laranjo S, et al. Assessment and effect of a gap between new-onset epilepsy diagnosis and treatment in the US. Neurology. 2019;92:e2197-e2208

10. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. Lancet. 2005;365:2007-13.

11. Wiebe S. An immediate antiepileptic drug regimen reduced short-term (2-y) recurrence of seizures more than a deferred regimen. ACP Journ Club. 2005;143:75.

12. Kho LK, Lawn ND, Dunne JW, Linto J. First seizure presentation: do multiple seizures within 24 hours predict recurrence? Neurology. 2006;67:1047-9.

13. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46:470-2.

14. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475-82.

15. Beretta S, Carone D, Zanchi C, Bianchi E, Pirovano M, Trentini C, et al. Long-term applicability of the new ILAE definition of epilepsy. Results from the PRO-LONG study. Epilepsia. 2017;58:1518-23.

16. Hakami T, McIntosh A, Todaro M, Lui E, Yerra R, Tan KM, et al. MRI-identified pathology in adults with new-onset seizures. Neurology. 2013;81:920-7.

17. Ho K, Lawn N, Bynevelt M, Lee J, Dunne J. Neuroimaging of first-ever seizure: Contribution of MRI if CT is normal. Neurol Clin Pract. 2013;3:398-403.

18. Tatum WO, Selioutski O, Ochoa JG, Clary HM, Cheek J, Drislane FW, et al. American Clinical Neurophysiology Society Guideline 7: Guidelines for EEG Reporting. Neurodiagn J. 2016;56:285-93.

19. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010;51:671-5.

20. Australian Bureau of Statistics. 2033.0.55.001 - Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia, Canberra, Autralia, 2013 [Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001].

21. Lawn N, Chan J, Lee J, Dunne J. Is the first seizure epilepsy--and when? Epilepsia. 2015;56:1425-31.

22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377-81.

23. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512-21.

24. Kim LG, Johnson TL, Marson AG, Chadwick DW. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. Lancet Neurol. 2006;5:317-22.

25. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993;80:27-38.

26. Askamp J, van Putten MJ. Diagnostic decision-making after a first and recurrent seizure in adults. Seizure. 2013;22:507-11.

27. Hauser WA, Rich SS, Annegers JF, Anderson VE. Seizure recurrence after a 1st unprovoked seizure: an extended follow-up. Neurology, 1990;40:1163-70

28. Chandramoulesswaran V, Dhanaraj M, Rangaraj R, Vengatesan A. Patients' preferences towards antiepileptic drug therapy following first attack of seizure. Neurol India. 2006;54:387-9.

29. Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. Neurology. 1997;49:991.

30. Leone MA, Giussani G, Nevitt SJ, Marson AG, Beghi E. Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure. Cochrane Database Syst Rev. 2016.

31. Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017;12:Cd011412.

32. Jacoby A, Gamble C, Doughty J, Marson A, Chadwick D. Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. Neurology. 2007;68:1188-96.

FIGURES AND TABLES

Figure 1: Treatment decisions at the time of diagnosis and during follow-up

Table 1: Baseline characteristics of patients with newly diagnosed epilepsy (n=610)

Table 2: Multivariable analysis of factors associated with treatment initiation at diagnosis

Table 3: Reasons for (A) therapy not being recommended by the treating neurologists and (B) patients declining therapy when recommended at diagnosis

Table 1: Baseline characteristics of patients with newly diagnosed epilepsy (n=610)

Characteristic	**Number (%)**
Male	372 (61.0%)
Age	Median: 40 years, range 15 – 88, IQR: 24-57
Socio-economic status	Median: 59th percentile, range: 1-100, IQR: 48-86
Ethnicity	
White	527 (86.4%)
Indigenous Australian (Aboriginal or Torres Strait Islander)	25 (4.1%)
Other	58 (9.5%)
Type of epilepsy	
Generalised	74 (12.1%)
Focal	373 (61.2%)
Unclassified/unknown	163 (26.7%)
Number of seizures at diagnosis	
1	184 (30.2%)
2	211 (34.6%)
3	93 (15.3%)
4	47 (7.7%)

5 or more	75 (12.3%)
EEG before diagnosis - Routine EEG - Sleep-deprived EEG - Prolonged video EEG (3 hours)	420 (68.9%) 420 71 1
Epileptiform EEG findings at diagnosis	145 (23.8%)
CT and/or MRI before diagnosis	433 (71.0%)
Epileptogenic neuroimaging at diagnosis	247 (40.5%) Previous stroke: 112 Post-traumatic gliosis: 55 Brain tumour: 45 Mesial temporal sclerosis/hippocampal atrophy: 16 Cortical malformation: 12 Perinatal insult: 6 Arachnoid cyst with mass effect: 1

IQR, interquartile range

Table 2: Multivariable analysis of factors associated with treatment initiation at diagnosis

Variable	**Odds Ratio**	**95% CI**		**P value**
Gender (reference = female)	1.26	0.85	1.86	0.25
Age (reference = 18 up to 65 years of age)				
<18 years of age	0.45	0.22	0.94	0.034
≥65 years of age	3.06	1.62	5.80	0.001
Socio-economic status	0.985	0.977	0.994	0.001
Epileptiform EEG results at diagnosis	0.79	0.47	1.33	0.37
Epileptogenic lesion on neuroimaging at diagnosis	2.15	1.26	3.68	0.005

Epilepsy Type (reference = generalised)				
Focal	0.93	0.44	1.96	0.86
Unclassified/unknown	0.82	0.38	1.79	0.62
Number of seizures before diagnosis (reference = 1)				
2	3.48	2.03	5.96	<0.001
3	2.71	1.43	5.14	0.002
4	3.91	168	9.12	0.002
5 or more	3.53	1.75	7.13	<0.001
Presence of tonic-clonic seizures before diagnosis	0.89	0.45	1.75	0.74
Seizure clusters (2 or more seizures occurring in the same day) occurring before diagnosis	2.57	0.21	0.73	0.002
Presence of lifestyle/external factors	0.67	0.46	0.97	0.033
Sleep status when seizures occurred (reference = awake)				
Not specified	0.98	0.53	1.78	0.94
Only asleep	0.1.04	0.63	1.72	0.87
Both awake and asleep	0.87	0.43	1.77	0.70
Having fewer than one seizure per year since first seizure prior to diagnosis	0.40	0.21	0.73	0.003

OR, odds ratio; CI, confidence interval

Table 3: Reasons for (A) therapy not being recommended by the treating neurologists and (B) patients declining therapy when recommended at diagnosis

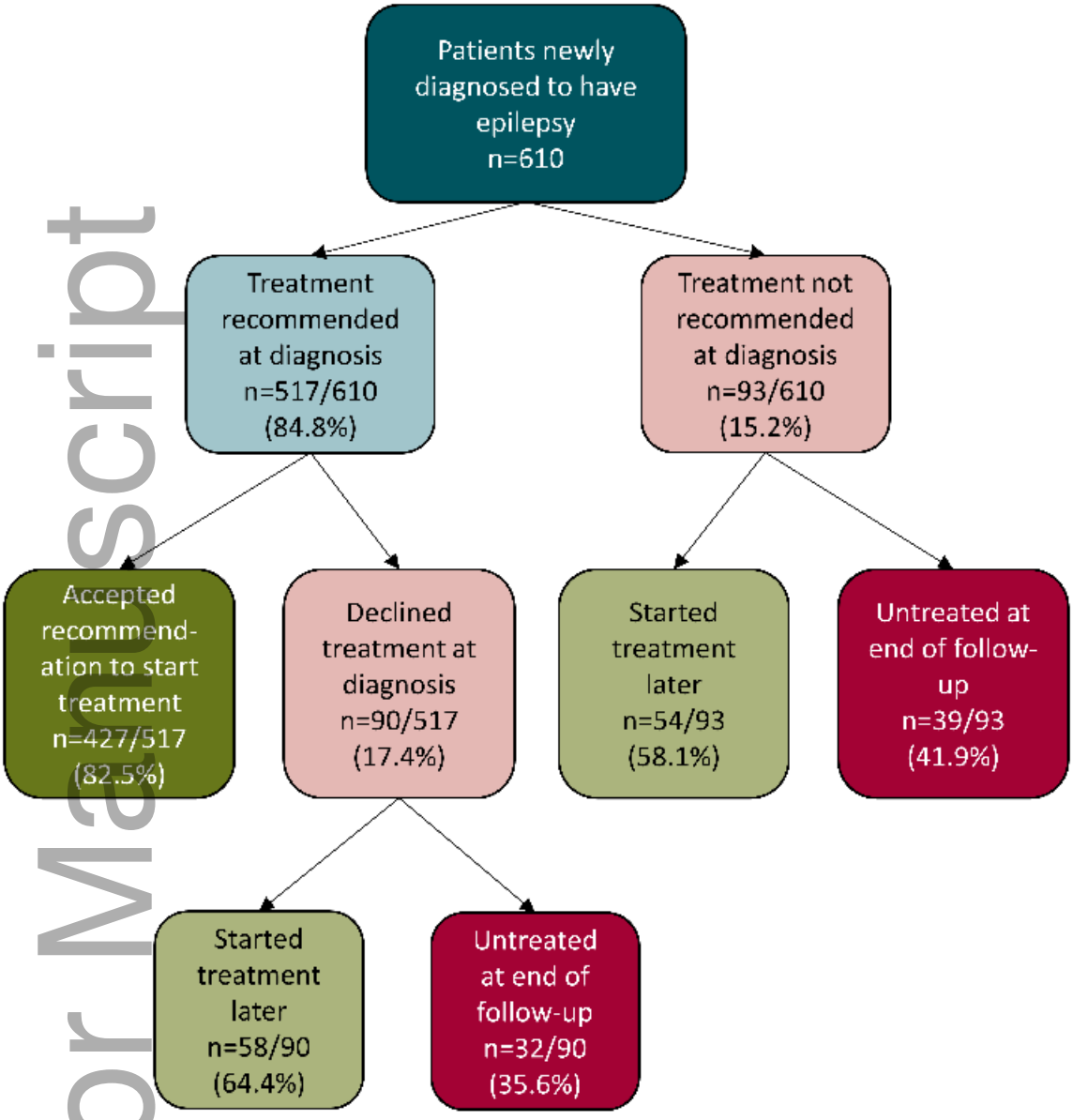
Table 3A

Reason for treatment not being recommended by neurologists (n=93)	**Number (%)**

Only single seizure	25 (27)
Awaiting further results	24 (26)
Presence of lifestyle/external factors	19 (20)
Infrequent seizures not thought to require treatment	14 (15)
No explicitly stated reason	10 (11)
Concern of medication interaction	4 (4)
Nocturnal sleep-only seizures not thought to require treatment	3 (3)
Neurosurgical review/intervention impending	3 (3)
Pregnancy	3 (3)
Neurologist believed patient unlikely to adhere to treatment	1 (1)

Table 3B

Reason for patients declining treatment (n=90)	**Number (%)**
Not convinced of necessity of treatment	40 (44)
Not convinced of diagnosis	16 (18)
Presence of lifestyle/external factors with seizures	12 (13)
No explicitly stated reason	11 (12)
Fear of adverse effects of anti-seizure medications	8 (9)
Nocturnal sleep-only seizures	4 (4)
Fear of medication interactions	2 (2)
Predominantly focal aware seizures not thought to require treatment	2 (2)
Patient pregnant/planning pregnancy	2 (2)
Infrequent seizures not thought to require treatment	1 (1)



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