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Anti-epileptic drug utilization pattern and control of seizure among patients with epilepsy at two tertiary hospitals in Addis Ababa, Ethiopia: A Hospital-based cross-sectional study

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Abstract

Background: Anti-epileptic drugs (AEDs) are the primary therapeutic modes for patients with epilepsy and have been demonstrated to control seizures, which decreases morbidity and mortality associated with epilepsy. There is a paucity of data on treatment outcomes among epileptic patients in resource-poor settings. The study aimed to evaluate the AED utilization pattern and control of seizures among patients with epilepsy on follow-up at St. Paul's Hospital Millennium Medical College and Amanuel Specialized Mental Hospital.

Methods: A hospital-based cross-sectional study involving direct patient interviews and medical record reviews were conducted to collect the data. Adherence of AED was measured using a Morisky Medication Adherence Scale-8 (MMAS-8), where patients with MMAS-8 scores of ≥6 were considered to be adherent. Factors affecting seizure control were determined using logistic regression analysis.

Results: From a total of 454 patients, 58.6% were men. The commonest type of seizure was generalized tonic-clonic seizure observed in 93.3% of patients. Monotherapy was prescribed in 83.7% of patients for the management of seizures, among which phenobarbitone was utilized in 51.3% of patients as a single anticonvulsant drug. Majority (61%) of patients with epilepsy had poor seizure control. About 65% of patients were adherent to their treatment and 39 % of the patients were seizure-free for at least one year. Only 177 (39.0%) patients had good control of seizures with no attack in the previous six months. Duration of AED therapy ≤5 years non-adherence were found to be independently associated with poor seizure control.

Conclusion: Based on our findings, the majority of patients with epilepsy were on monotherapy and had poor seizure control. Phenobarbitone and phenytoin were the frequently utilized AEDs. Duration of therapy less than 5 years and poor adherence were independently associated with an uncontrolled seizure. The findings collectively indicate that health care providers should focus on recently diagnosed patients and adherence to AEDs to control seizures.

Keywords: Anti-epileptic drug use, Epilepsy, Medication Adherence, Seizure control, Addis Ababa, Ethiopia

Background

Epilepsy is the second most common chronic neurological disorder characterized by recurrent seizures. Globally, 50 million people are estimated to live with epilepsy, of whom 80-90% are from developing countries, posing a huge social and economic burden to the poor.[1] The annual incidence of epilepsy ranges from 50-70 cases per 100,000 people at risk in industrialized countries and up to 190 per 100,000 in developing countries.[2] In Ethiopia, the annual incidence of epilepsy was reported to be 64 per 100,000 inhabitants at risk in community studies and was more frequent in males than females.[3] The incidence has a bimodal distribution with a peak in the first decade and a second peak in the elderly.[4, 5] Furthermore, the incidence is higher among people over 70 years of age as compared with those younger than 10 years.[4] Generalized tonic-clonic seizure was the most common seizure type and occurred in 69–81%. On clinical grounds, partial seizures occurred in 18–20%, and in one-third of these secondary generalizations were followed. Unclassifiable seizures occurred in 11% of cases.[6]

Several types of anti-epileptic drugs (AEDs) are used for the symptomatic management of epilepsy. Treatment is aimed at controlling seizures associated with minimal incidence of adverse drug reactions.[7] The keys for choice of AEDs are age, the underlying cause of the seizure, type of seizure, availability of a drug, affordable price, concurrent medical conditions, pharmacokinetic properties of individual AEDs and presence of precipitating factors.[8] Based on the recommendations of international guidelines, treatment should be started with a single conventional AED. The dose should be slowly built up until seizure control is achieved or side effects occur. If the initial treatment is ineffective or poorly tolerated, then another AED can be tried. The dose of the second drug is slowly increased until an adequate or maximum tolerated dose is reached. The first drug is then tapered off slowly. Combination therapy can be considered when two attempts at monotherapy with AEDs have not resulted in seizure freedom.[9] AED utilization pattern of several studies showed that single drug use (monotherapy) was the predominant strategy. The proportion of patients on monotherapy was 80.4% in Northwest Ethiopia[10], 62.1% in India[11], 53.7% in Brazil[12], 67% in Bangladish[13], 78% in Oman[14] and 74.4% in Colombia[15]. The frequently utilized AEDs were phenobarbitone and carbamazepine in 62.5% and 17.9%, respectively in Northwest Ethiopia.[10] However, phenytoin, sodium valproate and carbamazepine were more frequently used in studies from Bangladesh, Brazil, India, and Oman.[8,11-13] About 90% of patients with epilepsy in developing countries are not receiving appropriate treatment due to the cultural attitude, lack of prioritization, poor healthcare system, economic problems and inadequate supply of AEDs.[16-18] In Ethiopia, more than 85% of people living with epilepsy do not get epilepsy treatment. Ninety percent of the untreated were unaware of the existence of epilepsy treatment, while only 4% of them reported cost as a reason for not receiving treatment.[19- 20]

Epilepsy is associated with significant morbidity and premature death. Control of seizures is the main outcome measure in epilepsy treatment. Up to 70% of people with epilepsy could become seizure-free with appropriate diagnosis and treatment.[14] Treatment efficacy, achieved by AEDs, is counter-balanced by drug-related adverse effects, which were reported in 40-80% of individuals on AEDs. In previous studies, this high proportion of adverse events was the major reason for poor adherence and seizure control.[21, 23] Other factors associated with poor seizure control were male gender, monotherapy, presence of comorbidity and alcohol consumption.[23] To the best of our knowledge, there are few studies on the AED utilization and control of seizures among adults in Ethiopia. Moreover, most of them were retrospective studies that were associated with low quality of data. There is also a huge discrepancy in the magnitude of controlled seizure among patients receiving AEDs with a range from 8% to 93.8%.[10, 23, 24] This warrants the need for additional studies that look into the current treatment armamentarium of epilepsy in Ethiopia.

This study aimed to assess the AED utilization pattern and control of seizures among patients with epilepsy at St. Paul's Hospital Millennium Medical College (SPHMMC) and Amanuel Specialized Mental Hospital (ASMH). The data can also help to develop strategies to achieve a rational use of AEDs and better patient outcomes.

Methods

Stud setting and study design

This study was conducted at SPHMMC and ASMH in Addis Ababa, Ethiopia. SPHMMC is a public hospital and medical teaching college with an inpatient capacity of more than 392 beds and serves an average of 200,000 emergency and outpatient clients annually.[25] The hospital has a dedicated clinic for patients with epilepsy and serves an average of 60 patients with epilepsy every month. ASMH is the oldest mental health facility located in the central part of Addis Ababa. It has a total of 300 beds and provides outpatient service for an average of 115,000 patients each year.[26] It was established to serve with mental illnesses and victims of substance abuse. In addition, the hospital has a follow-up clinic for patients with epilepsy.

A hospital-based cross-sectional study was conducted to evaluate the AED utilization pattern and control of seizures among patients with epilepsy at SPHMMC and ASMH from April 1 to July 30, 2018.

Source population

All patients with epilepsy who visited the adult neurology clinics of SPHMMC and ASMH.

Study population

All patients with epilepsy visited the adult neurologic clinics of SPHMMC and ASMH from April 1 to July 30, 2018.

Sample size determination

The sample size was determined based on the single population formula for the infinite population with a 95% CI, 5% margin of error, and taking a 12.5% prevalence of epilepsy among patients visiting ambulatory neurologic clinics from a similar setting.[27] To allow for subgroup analysis, we amplified the sample size by 50% to reach a total of 502 patients with epilepsy. The total sample size was divided equally and distributed to the two hospitals.

Inclusion and exclusion criteria

Inclusion criteria

1. Patients aged 18 years and above with a diagnosis of epilepsy who visited the neurologic clinics of SPHMMC and ASMH.
2. Patients with epilepsy were taking AEDs for at least six months.
3. Patients with epilepsy who give written informed consent.

Exclusion criteria

Patients with unstable psychiatric illness and not accompanied by their next of kin or a regular caregiver.

Sampling method

Participants were recruited consecutively until the intended sample size was reached. All volunteered participants were interviewed by trained nurses during their clinic visits.

Operational definitions

Drug utilization pattern: Comprises of evaluation of type, number, dosage, rational use, adherence, the occurrence of adverse drug reactions and treatment outcome of AEDs based on the World Health Organization definition.[28]

Controlled seizure: considered when a patient on AED is free of seizure attacks for at least 6 months on the day of the interview.

Data collection tools and procedures

Data was collected using a structured questionnaire that was translated to a local language (Amharic) and pre-tested. The patient interview was aimed at gathering information related to socio-demographic, drug side effects, drug adherence and seizure control. Their medical records were reviewed for the type of seizure and prescribed AED.

Adherence to AEDs was measured using a Morisky Medication Adherence Scale-8 (MMAS-8). The MMAS-8 is a generic self-reported, medication-taking behavior scale, validated for hypertension but used for a wide variety of medical conditions. It consists of eight items focusing on past medication use patterns with a scoring scheme of “Yes” = 0 and “No” = 1 for the first seven items except item number five in which the values “Yes” and “No” were reversed and for the last item a five-point Likert response was used with options “never”, “once in a while”, “sometimes”, “usually”, and “always.” In this Likert scale, values ranging from 0 to 1 were given

at a specified interval of 0.25 with "0" given for "never" and "1" given for "always". The items were then summed to give a maximum score of 8. Accordingly, adherence was considered with a score of ≥ 6 and non-adherence was with a score of <6.[29, 30]

Statistical Analysis

All data were entered into EPI INFO version 6 then exported to and analyzed using Statistical Software for Social Sciences (SPSS) version 23. Descriptive statistics such as frequency, percentage, mean and standard deviation (SD) were employed to summarize the data. Univariate analysis was performed to relate each variable to seizure control status. Multivariable logistic analysis was used to assess the predictability of the independent variables and seizure control status and to estimate the odds ratios (OR) and 95% confidence intervals (CI). Finally, a p-value <0.05 in a multivariable model was considered significant.

Results

Baseline characteristics

Out of 502 study participants enrolled, 454 were a candidate for analysis. Of these, 266 (58.6%) participants were men. The mean age of the study population was 30.8 (standard deviation ± 12.9; range: 15–77) years, and over one-third (39.9%) lie in the age range of 15-24 years. The educational level of participants showed that 43.4% and 27.1% had primary and secondary education, respectively. More than half (56.4%) of participants were from Addis Ababa and 76.7% were employed. The sizable proportion (52.6%) of them had a very low monthly income <500 Ethiopian Birr. Two hundred fifty-eight (56.8%) participants had epilepsy for more than 5 years. With regards to the duration of AED therapy, 24.4% and 49.2% of the participants were on treatment for 2 to 5 years and more than 5 years, respectively. The mean duration of epilepsy and AED therapy was 8.8 and 7.4 years, respectively. Generalized tonic-clonic seizure (GTCS) was the predominant type of epilepsy reported in 451 (99.3%) participants. The commonest comorbidities reported were Human Immuno-deficiency Virus (HIV), hypertension, and psychiatric disorders in 1.8%, 1.6%, and 1.3% of participants, respectively [Table 1].

Table 1: Baseline characteristics of participants at SPHMMC and ASMH, Addis Ababa, Ethiopia, 2018 (n=454)

Variable	Category		Number	%
Age (years)	15-24		181	39.9
	25-34		148	32.6
	35-44		63	13.9
	45-54		27	5.9
	55-64		19	4.2
	≥ 65		16	3.5
Sex	Male		266	58.6
	Female		188	41.4
Marital status	Single		286	63.0
	Ever married		168	37.0
Educational status	Unable to read and write		33	7.3
	Read and write		60	13.2
	Grade 1-8		137	30.2
	Grade 9-12		123	27.1
	Higher education		101	22.2
Occupation	Unemployed		106	23.3
	Employed		348	76.7
Monthly income (ETB)	<500		239	52.6
	≥500		215	47.4
Type of Seizure	Generalized tonic-clonic	Focal	451	99.3
	Other		2	0.4
			1	0.2
Comorbidity	Hypertension		7	1.6
	Diabetes mellitus		1	0.2
	HIV		8	1.8
	Psychiatric disorder		6	1.3
	Other	None	2	0.4
			430	94.7
Duration of the seizure (years)	<5		159	35.0
	5-10		174	38.3
	≥10		121	26.7
Duration of AED therapy (years)	<5		199	43.8
	5-10		163	35.9
	≥10		92	20.3
Adherence to AED	Good		293	64.5
	Poor		161	35.5

Abbreviation: AED, anti-epileptic drug; ASMH, Amanuel Specialized Mental Hospital; ETB, Ethiopian birr; SPHMMC, St. Paul's Hospital Millennium Medical College; SD, standard deviation

The pattern of AED utilization

Three hundred-eighty (83.7%) of participants were on monotherapy while 71 (15.6%) were on combination therapy with two AEDs. Among drugs utilized as monotherapy, phenobarbitone was used by 233 (51.3%) and phenytoin was used by 88 (19.4%) participants. The most frequently prescribed combination therapy was phenobarbitone plus phenytoin in 26 (5.7%) participants followed by phenobarbitone plus carbamazepine in 17 (3.7%) participants. Among the newer AEDs, only lamotrigine was used by 1 (0.2%) patient. Among those on combination therapy, two drugs were utilized more frequently than three drugs (15.6% Vs 0.7%) [Table 2].

Table 2: Treatment pattern of antiepileptic drugs among study participants at SPHMMC and ASMH, Addis Ababa, Ethiopia 2018 (n=454)

Treatment	Number	%
Number of AED used		
Monotherapy	380	83.7
Two drugs	71	15.6
Three drugs or more	3	0.7
Monotherapy		
PHT	88	19.4
PHB	233	51.3
CBZ	39	8.6
VPA	19	4.2
LTG	1	0.2
Combination Therapy		
PHB+PHT	26	5.7
PHB+CBZ	17	3.7
PHB+VPA	10	2.2
PHT+CBZ	5	1.1
PHT+VPA	2	0.4
CBZ+VPA	11	2.4
PHB+PHT+CBZ	2	0.4
PHB+CBZ+VPA	1	0.2

Abbreviation: AED; anti-epileptic drug; PHB, phenobarbitone; PHT, phenytoin; CBZ, carbamazepine; VPA, sodium valproate; LTG, lamotrigine; ASMH, Amanuel Specialized Mental Hospital; SPHMMC, St. Paul's Hospital Millennium Medical College

The most frequently used AEDs in monotherapy or combination therapy were phenobarbitone, phenytoin, and carbamazepine in 289 (63.6%), 123 (27.1%), and 43 (9.5%) patients, respectively. [Figure 1].

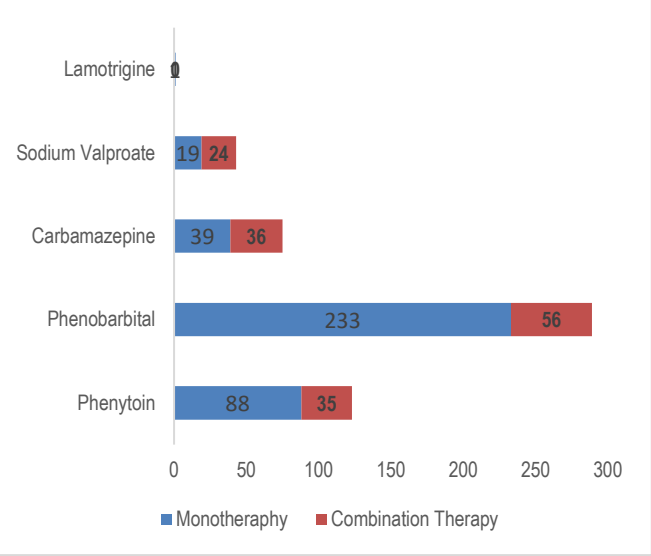

Figure 1: Frequency of antiepileptic drug use in monotherapy or combination therapy, therapy at SPHMMC and ASMH, Addis Ababa, Ethiopia, 2018.

Adverse drug reactions with AED monotherapy

From a total of 380 patients on monotherapy, adverse drug reaction (ADR) was observed among 328 (86.3%) of them. Phenobarbitone was the most common drug to cause ADR observed in 186 (48.9%), especially in the form of gastrointestinal symptoms and central nervous system (CNS) manifestations. Phenytoin was the second most common drug to cause ADR reported in 87 (22.9%) of patients. The detail of the category and type of reaction is given in Table 3.

Seizure control status and associated factors

Overall, 177 (39.0%) patients had good control of seizures with no attack in the previous six months. The duration of AED for less than 5 years was significantly associated with poor seizure control as compared to those on AED for 5 years or more (Adjusted Odds Ratio [AOR], 2.45; 95% Confidence Interval [CI], 1.51-3.99; $p < 0.001$). Poor adherence to AEDs was also independently associated with poor seizure control as compared to good adherence (AOR, 1.75; 95 CI, 1.14-2.70; p=0.01). However, age, sex, marital status, duration of seizure, comorbidity and number of AED utilized were not associated with seizure control [Table 4].

Discussion

The present study attempted to evaluate the AED utilization pattern and control of seizures among patients with epilepsy at SPHMMC and ASRH. The study revealed that 83.7% of patients with epilepsy were on a single AED, among which phenobarbitone and phenytoin were prescribed in 51.3% and 19.4% of them respectively. Similarly, phenobarbitone and phenytoin were the most frequently used AEDs in combination therapy. Good seizure control with no attack in the previous six months was achieved in only 39% of patients. Duration of therapy less than five years and poor adherence to AEDs were independently associated with poor seizure control. This study revealed that 83.7% (95% confidence interval, 80.4-87.2) of patients with epilepsy were on a single AED. This finding is consistent with the recommendations of international guidelines.[31-33] Similarly, monotherapy was the preferred treatment modality in other studies.[13, 31, 34-36]

Monotherapy was utilized by 62-96% of patients in the United Kingdom, Saudi Arabia, Taiwan and India. Phenobarbitone was used as the first-line AED in the current study. This does not comply with the recommendation by the Ethiopian national treatment guideline, where phenobarbitone was listed as a second-line drug.[37] The frequently utilized first-line AEDs in several studies [8, 11-14] include: phenytoin in India and Brazil,[11, 12] carbamazepine in Bangladish[13] and Sodium valproate in Oman and Colombia.[8, 14]

Table 3: Adverse drug reactions reported with AED monotherapy at SPHMMC and ASMH, Addis Ababa, 2018 (n=380)

Type of Reaction		AED				
		PHT N (%)	PHB N (%)	CBZ N (%)	VPA N (%)	LTG N (%)
Mouth	Gum hypertrophy	4 (1.1)	-	-	-	-
GIT	Nausea, vomiting, epigastric pain	12 (3.2)	50 (13.6)	6 (1.6)	6 (1.6)	-
CNS	Headache, irritability, drowsiness, ataxia, confusion, forgetfulness	56 (14.7)	110 (28.9)	25 (6.6)	12 (3.2)	1 (0.3)
Skin	Rash, urticaria, photosensitivity	3 (0.8)	-	-	-	-
Musculoskeletal	Weakness	12 (3.2)	26 (6.8)	3 (0.8)	2 (0.5)	-
Total		87 (22.9)	186 (48.9)	34 (8.9)	20 (5.3)	1 (0.3)

Abbreviation: AED; anti-epileptic drug; N, number; PHB, phenobarbitone; PHT, phenytoin; CBZ, carbamazepine; VPA, sodium valproate; LTG, lamotrigine; GIT, gastrointestinal tract; CNS, central nervous system; ASMH, Amanuel Specialized Mental Hospital; SPHMMC, St. Paul's Hospital Millennium Medical College

The failure to follow the national treatment guideline in our study might be due to the cost and unavailability of first-line AEDs like sodium valproate and carbamazepine in the country. Furthermore, the selection of drugs was different in different studies, which could be due to the variations in local guidelines. This lack of uniformity and non-compliance with the recommendations of international guidelines need further study to find out the reason for the disparity. Regarding seizure control, our study showed that only 39% of patients were found to be free of seizure for the last six months follow-up period. This figure was comparable with reports from previous reports from Ethiopia.[30, 37-39] However, in studies by Gurshaw M et al.,[41] Rawat C et al.[42] and Alsfouk BA et al,[43] seizure was controlled in 57%, 60%, and 78,6% of patients respectively. The discrepancy might be due to the differences in the type of AED prescribed to control seizures. The selection of drugs was variable in different studies due to variations in resource availability and local guidelines. Several factors may contribute to uncontrolled seizures at epilepsy clinics. Of these; poor adherence, misdiagnosis,

Table 4: Factors associated with poor seizure control at SPHMMC and ASMH in a multivariable logistic regression model, Addis Ababa, Ethiopia, 2018

Variable		No. of cases with poor seizure control/ No. of total cases (%) 277/454 (61.0)	COR (95% CI)	P value	AOR (95% CI)[a]	P value
Age, years	< 40	225/365 (61.1)	1.1 (0.7-1.8)	0.63	1.0 (0.56-1.78)	0.99
	≥ 40	52/89 (58.4)			1	
Sex	Men	157/266 (59.0)	0.8 (0.5-1.2)	0.33	0.9 (0.58-1.32)	0.53
	Women	120/188 (63.8)			1	
Marital Status	Married	93/168 (55.4)	1.5 (0.9-2.1)	0.07	0.8 (0.50-1.26)	0.32
	Unmarried	184/286 (64.3)			1	
Address	Outside AA	115/198 (58.1)	1.2 (0.8-1.8)	0.29	0.8 (0.51-1.16)	0.22
	AA	162/256 (63.3)			1	
Educational Status	Unable to read or write	24/33 (72.7)	1.8 (0.8-3.9)	0.20	1.87 (0.79-4.44)	0.15
	Able to read and write	36/60 (60.0)			1	
Occupation	Employed	205/348 (58.9)	0.7 (0.4-1.0)	0.11	0.7 (0.42-1.13)	0.14
	Unemployed	72/106 (67.9)			1	
Duration of Seizure, years	< 10	196/302 (64.9)	1.6 (1.1-2.4)	0.02	1.0 (0.62-1.68)	0.94
	≥ 10	81/152 (53.3)			1	
Duration of AED, years	< 5	145/201 (72.1)	2.4 (1.6-3.5)	<0.001	2.5 (1.51-3.99)	<0.001
	≥ 5	132/253 (52.2)			1	
Optimal AED dose	No	240/396 (60.6)	0.9 (0.5-1.5)	0.70	1.0 (0.52-1.78)	0.91
	Yes	37/58 (63.8)			1	
Adherence to AED	Poor	113/161 (70.2)	1.9 (1.2-2.8)	0.003	1.8 (1.14-2.70)	0.01
	Good	164/293 (56.0)			1	
AED side-effect	Present	171/270 (63.3)	1.3 (0.9-1.9)	0.24	1.2 (0.82-1.85)	0.31
	Absent	106/184 (57.6)			1	
Comorbid illness	Present	16/24 (66.7)	1.3 (0.5-3.1)	0.70	1.2 (0.45-2.88)	0.75
	Absent	261/430 (60.7)			1	
Number of AED used	Monotherapy	228/380 (60.0)	0.8 (0.5-1.3)	0.40	0.6 (0.37-1.12)	0.12
	Combination therapy	49/74 (66.2)			1	

AA, Addis Ababa; AED, anti-epileptic drug; 1, reference variable; COR, crude odds ratio; AOR, adjusted odds ratio; NA, not applicable; [a] Adjusted for age, sex, marital status, address, educational status, duration of seizure, and duration of anti-epileptic drug use

misclassification of the seizure, a suboptimal dose of AED, and the presence of untreated comorbid illness.[44, 45] Our study also showed a significant association between non-adherence and poor seizure control.

The study has some limitations. First, it was a cross-sectional study with no prospective follow-up period. As a result, it may be subjected to recall bias. Second, it was a hospital-based study and may not fully represent the situation in the community. Third, it involved only two tertiary-care centers, which might not represent the overall epilepsy clinics in the country. Therefore, a large-scale nationwide study is highly recommended.

In conclusion, the findings of our study revealed that AED monotherapy is still the most frequently utilized therapeutic strategy among adults with epilepsy. Phenobarbitone was the most commonly prescribed AED. The majority of patients had poor seizure control and the duration of treatment was less than five years and poor adherence to AEDs was independently associated with poor seizure control.

Therefore, particular attention should be given to recently diagnosed patients and on adherence to improve the control of seizures. More AEDs should also be available at an affordable price as per the recommendations of the national treatment guideline.

Furthermore, a prospective multi-center study is warranted to establish the cause-effect relationship between the predictor variables and seizure control.

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Authors' contributions

TB conceived and developed the study proposal. Both authors were equally involved in the interpretation, analysis, and write-up of the final manuscript.

Competing interests

None.

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