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Pharmacological outcomes in teenagers with newly diagnosed epilepsy: a 30-year cohort study

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Summary and key words

Objective: To evaluate the long-term pharmacological outcomes in teenagers with different epilepsies.

Method: This study included teenagers aged 13 to 19 years at treatment initiation who were newly treated with antiepileptic drugs (AEDs) at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland between 1 Sep 1982 and 30 Sep 2012. Patients were prospectively followed till 30 April 2016 or death, with at least a two-year follow-up.

Results: A total of 332 adolescent patients (53% female; median age 16 years; 54% generalised epilepsy) were included. At the end of the study, 221 (67%) patients were

seizure-free. A higher seizure-free rate was observed in those with generalised compared to focal epilepsy (72% vs 60%, P=0.01). During the study, 108 patients had relapses after periods of being seizure-free, most commonly due to poor adherence to AEDs (49%, n=53/108). AED withdrawal was associated with a high risk of seizure recurrence (70%, n=26/37), but 56% (n=61/108) of relapsed patients became seizure-free again by the end of study, with only 9% (n=31/332) meeting the ILAE definition of pharmacoresistance during follow-up. Of the 221 seizure-free patients, 83% achieved this on monotherapy. There was no significant difference in efficacy rate between new and standard AED monotherapy (74% vs 77%, P=0.66). Overall poor tolerability rate of AEDs was 21% (n=69/332). Among the different new and standard AEDs used as the initial monotherapy, lamotrigine was associated with the lowest rate of adverse effects (12%, n=15/124), while topiramate was associated with the highest rate (56%, n=5/9).

Significance: Teenagers with epilepsy showed good seizure control, particularly those with generalised epilepsy. However, relapse was common and there was high risk of seizure recurrence after treatment withdrawal. Most patients were controlled on monotherapy. As the efficacy of AEDs was comparable, tolerability can be a primary consideration for AED selection in this population.

Key Words: Adolescents, Antiepileptic drugs, Efficacy, Tolerability, New onset epilepsy.

Key points

- Most teenagers with different newly diagnosed epilepsies demonstrated good seizure control, particularly those with generalised epilepsies
- Although most patients were pharmaco-responsive, relapse was common
- The majority of patients were controlled on monotherapy usually at moderate dosages
- There was no significant difference in the efficacy rate among different AEDs
- The frequency and type of adverse events varied among different AEDs

Introduction

Teenagers with epilepsy are a population that deserves special attention, as adolescence is often challenging, even for healthy adolescents. The presence of a chronic illness, such as epilepsy, may pose additional difficulties in this population.[1] Epilepsy and antiepileptic drugs (AEDs) have impacts on psychosocial function, learning capacity, career development, use of alcohol and recreational drugs, sexual activity, and pregnancy. Additionally, adherence to medications and adverse effects of AEDs (such as cosmetic problems, bone health, teratogenicity, and effects on cognition and behaviour) are also important issues in teenagers. These factors, in turn, can influence outcome.[2] Some newer AEDs may have better tolerability than older drugs.[3] Therefore tailoring drug selection is particularly important in this population.

Few observational studies have evaluated pharmacological outcomes in teenagers with different epilepsies; some studies have included teenagers with adults [4] or focused on particular epilepsy types.[5] This study aimed to evaluate long-term outcomes in teenagers with different epilepsies. Where possible treatment outcomes in this population were compared to previously published outcomes in adults.

Methods

Patients

This study included consecutive patients aged 13 to 19 years at treatment initiation, who were first diagnosed with epilepsy and prescribed AED treatment at the Epilepsy Unit of the Western Infirmary and subsequently at the West Glasgow Ambulatory Care Hospital

(WGACH) in Glasgow, Scotland. Patients were referred mainly from primary care with a minority (10%) coming from accident and emergency services. The patients started AED treatment between September 1982 and September 2012. They were prospectively followed up until 30 April 2016, or death, with at least a two-year follow-up after initiation of AED treatment.

Data were collected in the course of standard clinical care. At the first clinic visit, general physical and neurological examinations were performed. Additionally, clinicians used a predesigned questionnaire to collect demographic and clinical information from patients, family and witnesses. Investigations were performed as clinically indicated including electroencephalography (EEG) and brain imaging i.e. computed tomography (CT) scan and/or magnetic resonance imaging (MRI). These investigations supported the diagnosis and classification of the epilepsy, as well as screening for underlying structural abnormalities. These data subsequently helped to select the most appropriate AED.

Patients who had exhibited persistent poor treatment adherence unrelated to drug efficacy or tolerability, those who were thought to have seizures only because of alcohol intake or recreational drug use, and those presenting with non-epileptic seizures were excluded from the study.

Treatment approach

Treatment selection was based on the efficacy of the AED for a given seizure type or syndrome, the patients' characteristics (such as age, gender, comorbidities and concomitant drugs), and on the pharmacokinetics and tolerability profiles of the AEDs.[6,7] In practice, the AED was usually initiated after two or more unprovoked seizures had occurred more than 24 hours apart, but patients who experienced one seizure with evidence of an epileptogenic lesion in the brain that increased the probability of further seizures could be offered AED therapy.[8,9]

Patients were subsequently evaluated at the epilepsy clinic every six weeks for the first six months and every four months thereafter. At each visit, clinical information and the response to AED therapy were recorded. Patients were asked to record their seizure

number and descriptions using customised charts. Drug doses were adjusted as clinical circumstances indicated with attention paid to efficacy and tolerability.

Adherence was evaluated by directly questioning the patient at each visit and measuring blood drug levels whenever possible. Patients with persistently poor adherence to AEDs were excluded from this study, while those with intermittent poor adherence, who missed their medication occasionally, were included and the reasons for this were recorded.

Initial monotherapy was prescribed for all the patients included in the study. Then, where necessary, treatment regimens were modified based on response to treatment. Generally, if the initial AED was poorly tolerated at a low dose or failed to improve seizure control, it was replaced with an alternative. If the first AED was tolerated and significantly improved seizure control, but did not completely provide seizure freedom, combination therapies were usually recommended.[9]

Definitions

The latest terminology and classification of seizures and epilepsy of the International League Against Epilepsy (ILAE) were used.[10,11] Epilepsy was broadly classified as generalised or focal according to the putative cause and depending on factors such as age, seizure type, family history, interictal electroencephalographic changes, and the presence or absence of a potential epileptogenic lesion or injury visible on brain imaging. Generalised epilepsies, such as juvenile absence epilepsy and juvenile myoclonic epilepsy, were presumed to be of genetic origin. Based on clinical information and results of investigations, focal epilepsy was regarded as resulting from either demonstrated epileptogenic lesions (i.e. structural aetiology) or underlying but unidentified focal abnormalities (i.e. unknown aetiology). The clinical team making the diagnosis and selecting medication were epilepsy specialists and trainee neurologists.

Seizure-freedom was defined as a patient experiencing no seizures for the previous 12 months or longer. Relapse represented a seizure recurrence after a seizure-free period of at least 12 months. Pharmacoresistance represents failure of adequate trials of two tolerate and appropriately chosen and used AEDs schedule (monotherapy or polytherapy) to achieve

seizure-freedom for 12 months.[12] Tolerability of the first AED monotherapy was assessed. Intolerable adverse effects were those that caused withdrawal or dose reduction of the culprit AED. The adverse effects were recorded based on patient complaints and clinical judgments by epilepsy specialists. Mortality was examined; cases were categorised into SUDEP (sudden unexpected death in epilepsy), probable SUDEP and not SUDEP.[13] Treatment outcomes for patients who died or were lost to follow-up were assessed up to the last clinic visit.

An AED regimen was defined as either a single drug (monotherapy) or a combination of two or more drugs. The first AED regimen was always monotherapy, while all subsequent regimens could be an alternative monotherapy or a dual therapy combining the first AED with a second medication. New AEDs were those introduced into clinical practice from 1989 onwards. Medication dosage was recorded as daily dosage in milligrams based on the dose administered to the patient at the last follow-up or the dosage at which the patient discontinued treatment.

Statistical analysis

Microsoft Excel 2016, Minitab 17 Statistical Software, and GraphPad Prism 5 were used for data analyses. Categorical data were summarised using frequency counts and percentage. Continuous data were summarised using median, interquartile range (IQR), and range. A chi-square (X^2) test was conducted to assess the association of the categorical data. The Mann-Whitney test was applied for a comparison of the non-parametric continuous data.

Results

Patient demographics

A total of 332 newly diagnosed patients (176, 53% female) were included in this study and their clinical characteristics are summarised in Table 1. Their median age at treatment initiation was 16 years (range 13-19; IQR 15-18). The median duration of follow-up after treatment initiation was 4 years (range 2-31; IQR 2-9 years). Fifty patients had a family history of epilepsy (15%) and 19 patients had a learning disability (6%).

Epilepsy was classified as generalised in 178 (54%) patients and focal in 154 (46%). Epilepsy aetiology was classified as genetic in 178 (54%) patients, structural in 40 (12%), and unknown in 114 (34%). Epilepsy syndrome was classified as epilepsy with generalised tonic clonic seizure alone in 109 (33%) patients, juvenile myoclonic epilepsy in 58 (17%), juvenile absence epilepsy in nine (3%), and genetic epilepsy with febrile seizures plus and progressive myoclonus epilepsy in one each.

Seizure outcomes at the last follow-up

A total of 221 (67% of 332) patients were seizure-free at the end of the study. The patients were seizure-free for 12 years on average (median 12; range 1-30; IQR 7-15). Of controlled patients, 126 achieved seizure-free early within 12 months of starting treatment, including 83 patients who became seizure-free immediately after starting treatment (i.e. experienced no seizure on treatment). The remaining patients achieved seizure-freedom after 12 months of starting AED treatment. A higher number of patients with generalised epilepsy (n = 129/178; 72%) remained seizure free than those with focal epilepsy (n =92/154; 60%; 95% confidence interval [CI] for the difference between two proportions: 0.02–0.23; P=0.01). One hundred and eleven (33%) patients continued to have seizures at the last follow-up, with 64 patients never having been seizure-free for any 12 months during follow-up.

A total of 108 patients had relapses (i.e. a seizure recurrence after a period of seizure-freedom for at least 12 months), of which, 74 (69%) patients had one relapse and 34 (31%) had two or more relapses. Sixty-one (56%) patients, who had previous relapses during follow-up, ultimately achieved seizure-freedom for 12 months or more at the last follow-up (39 patients had one relapse and 22 had two or more relapses). Forty-seven (44%) relapsed patients continued to experience seizures at the last follow-up (35 one relapse and 12 two or more relapses). Thirty-three (31%) patients reported no clear reason for their relapse. The remaining reported one or more reasons as following: 53 poor adherence to AED (26 self-stopped their AED after long-term seizure-freedom, 27 missed or forgot doses), 14 were sleep deprived, 12 had comorbidities (e.g. infection, depression), and seven blamed “stress”.

Thirty-seven patients discontinued their AED in an attempt to come off treatment after being seizure-free for a long period, but only 11 (30%) remained seizure-free after successful withdrawal of AEDs, whereas the remainder relapsed and restarted treatment.

During the follow-up, 31 (9%) patients met the ILAE definition of pharmacoresistance. Among them, 7 (23%) ultimately became seizure-free (1 early, 6 delayed), and 24 (77%) continued to have seizures at the last follow-up (18 never achieve seizure-freedom, 6 had relapsed).

Final antiepileptic drugs

Among the 332 final AED therapies, 244 (74%) were monotherapy and 88 (26%) regimens were polytherapy. Of monotherapy, 136 (56%) patients took newer AEDs, while the remaining 108 (44%) were on standard drugs.

Of the 221 seizure-free patients, 184 (83%) achieved this by taking monotherapy (or last AED was monotherapy), while 37 (17%) were controlled on a combination of two to four AEDs. In 184 controlled patients taking monotherapy, no significant difference was observed in the efficacy rate between new AEDs (74%, 101/136) and standard drugs (77%, 83/108; 95% CI for the difference between two proportions: -0.11–0.19; P=0.66).

A total of 139 patients (42% of 332) achieved seizure freedom on their first AED, and 46 patients (29% of 159) were controlled on a second regimen. When combined, the first and second regimens accounted for 185 of the 221 patients (84%), who achieved seizure freedom. Seizure-free rates then decreased with subsequent AED regimens.

Lamotrigine was the most frequent continued monotherapy (n=79), followed closely by valproate (n=72). Carbamazepine (n=36) and levetiracetam (n=30) were also frequently employed monotherapies. There was no significant difference observed in the efficacy rates among different AED monotherapies in the cohort of mixed epilepsies, and in the subgroup analyses of generalized and focal epilepsies (Table 2).

Figure 1 demonstrates the dosages of lamotrigine, valproate, carbamazepine and levetiracetam monotherapies in controlled and uncontrolled patients. Doses in the uncontrolled group was significantly higher than in the controlled group for each AED.

Combination AEDs therapies were also evaluated. Dual therapies of lamotrigine/valproate, lamotrigine/levetiracetam, and lamotrigine/zonisamide were the most frequent continued regimens (n=17, 12, and 6, respectively). Among these duotherapies, the lamotrigine/levetiracetam regimen was associated with the highest seizure-free rate (75%, n=9), followed by lamotrigine/zonisamide (50%, n=3), while lamotrigine/valproate was associated with the lowest efficacy rate (47%, n=8). However, these differences were not statistically significant (p-value=0.3).

Twenty-four (7% of 332) patients were off-medication at the last follow-up, 16 (67%) of whom remained seizure free, while the remainder were uncontrolled. The controlled patients were seizure-free off medication for 13 years on average. Long-term remission was the main reason for drug discontinuation (n=11). One patient achieved long-term remission after epilepsy surgery. Another three female patients, who were seizure-free for a long period of time, had concerns about teratogenicity as they were planning to start a family. Adverse drug reactions alone (n=3) or with drug ineffectiveness (n=3) were also causes of treatment withdrawal. The remaining seven patients stopped their AED therapy for other reasons.

Tolerability of first antiepileptic drug

Of 332 initial AED monotherapies, 69 (21%) were associated with intolerable adverse effects (i.e. adverse effects resulted in drug withdrawal or dose reduction). As demonstrated in Table 3, there was significant differences in the tolerability rates of different AEDs. Lamotrigine was associated with the lowest adverse effect rate, while topiramate was associated with the highest rate.

Sixty-nine patients reported at least one intolerable adverse event, with a total of 97 overall being reported. Most commonly reported adverse effects were psychiatric problems, including mood disorders, aggression, behavioural problems, irritability and paranoid

ideation. Psychiatric problems accounted for 24% (n=23/97) of intolerable adverse reactions, levetiracetam being the culprit in more than half of cases. Sedation was the second most frequent complaint, followed by skin rash. Table 4 shows the different adverse effects associated with AED use.

Teratogenicity

During the follow-up, 17 female patients had 25 pregnancies: eight healthy babies, two unhealthy, one miscarriage. Data on the remaining babies and other pregnancies were unavailable. Of two unhealthy babies, one had spinal bifida and had been exposed to a combination of valproate/lamotrigine/levetiracetam/clobazam; daily doses in milligram were 1200/200/2000/10, respectively. Another baby had autism and was exposed to valproate 1000mg/day. During four pregnancies, patients self-stopped their AEDs.

Female adolescents (n=26/176; 15%) were prescribed valproate as their first AED significantly less often than male patients (n=55/156; 35%; 95% CI: 0.112-0.297, P < 0.001).

Mortality

Four (1.2% of 332) patients died during follow-up. Three deaths were due to SUDEP or probable SUDEP (0.9% of 332, 75% of all deaths), while one case of death was due to primary pulmonary hypertension. All SUDEP cases were female, aged 21, 22, and 23 years, with a duration of epilepsy of nine years for two patients and four years for the third. All SUDEP patients had primary generalised tonic clonic seizures, uncontrolled, and none had a learning disability. Two patients were on combination of lamotrigine and levetiracetam, while one patient was taking lamotrigine and gabapentin.

Discussion

This study evaluated the pharmacological outcomes in a cohort of teenagers with different newly diagnosed epilepsies. Patients were followed up at a single epilepsy centre over a 30-year period. This analysis showed an overall 1-year seizure-free rate of 67%. This was slightly higher than the seizure-free rates reported in two previous analyses of a cohort of mixed adults and adolescents from same epilepsy centre, in which the seizure control was

64% in 2000 and 2018.[14,15] However, the seizure freedom rate in this analysis was comparable to rate (68%) observed in the analysis on the same expanding cohort conducted in 2012.[9] The remission rate was also estimated to be 68% in an observational population-based study of adults with newly diagnosed epilepsy.[16]

In the present study, patients with generalised epilepsy reported a better response to AED treatment than those with focal epilepsy (72% vs 60%). Other studies have also demonstrated a high remission rate of adolescent-onset generalised genetic epilepsies (80%),[5] particularly for juvenile myoclonic epilepsy (90%).[17]

Patients in this study showed different courses of response to AED therapy. One quarter of patients achieved immediate, complete seizure control, 13% experienced some seizures but entered a seizure-free period within 12 months of starting treatment, and 29% became seizure-free after 12 months of treatment. Overall 19% of patients never achieved any 1-year seizure freedom during follow-up. Another 14% relapsed after being seizure-free for at least 1-year and continued to have seizures at the end of the study. The majority of patients were pharmaco-responsive. Only 9% met the ILAE definition of pharmcoresistance during follow-up, while the remaining uncontrolled patients failed only one AED or fewer due to lack of efficacy.

One third of patients experienced at least one relapse during follow-up, but re-entering remission was common (56%). The most common reason for relapse was poor adherence to AED therapy. Adherence was as important issue in our adolescent population. In addition to simple forgetfulness, many teenagers may feel stigmatised by taking an AED therapy.[2,18] Several potential solutions have been suggested to improve adherence in adolescent with epilepsy, such as technology-focused adherence interventions.[19]

This study demonstrated a high risk of seizure recurrence after drug withdrawal. Teenagers appeared to have the highest risk for seizure relapse following drug discontinuation compared to adults and children,[20] as age-related syndromes have a different prognosis. For example, childhood absence epilepsy shows a good prognosis for AED discontinuation, while juvenile myoclonic epilepsy, which is common in adolescence, is associated with a high risk of recurrence.[4]

The present study showed that a high proportion of patients were taking a single AED at the last follow-up. Furthermore, more than half of these final monotherapies were newer AEDs such as lamotrigine and levetiracetam. However, the use of standard AEDs, such as valproate and carbamazepine, remained frequent.

Seizures in the majority of patients were controlled on monotherapy. Moreover, most controlled patients achieved seizure freedom on their first or second AED regimen. The proportion of controlled patients reduced noticeably with each unsuccessful AED regimen thereafter. A comparable response rate to new and standard AEDs was observed. Furthermore, different monotherapies showed similar efficacy rates in the cohort of mixed epilepsies and in the subgroups of generalised and focal epilepsies. Not surprisingly, doses of AEDs were significantly lower in the controlled group than uncontrolled group, reflecting more aggressive use of AEDs in patients with intractable epilepsy. Mohanraj and Brodie [21] found that seizures were often controlled at modest or moderate doses.

Overall the poor tolerability rate of the first AED monotherapy was 21%. The most common adverse effects associated with AED use in adolescents were psychiatric problems, followed closely by sedation. Lamotrigine showed the best tolerability, while topiramate was associated with the highest rate of adverse effects. Indeed, lamotrigine has consistently demonstrated a better tolerability than most other AEDs in several studies, whereas topiramate has shown inferior tolerability.[22-25] In addition to differences in rate of tolerability, each AED demonstrated a distinct tolerability profile. Levetiracetam was poorly tolerated commonly due to psychiatric and behavioural adverse effects; lamotrigine was frequently discontinued due to skin reactions; while valproate was commonly associated with cosmetic adverse effects. These distinct adverse effect profiles can affect each patient differently. Therefore, tolerability offers an opportunity for tailoring AED selection.

It seemed that there was a shift away from valproate prescribing in women of childbearing age due to teratogenicity concerns. Indeed, females were prescribed valproate as first AED significantly less than males This may have affected the seizure-free rate in the generalised epilepsy patients. Male patients with generalized epilepsy (n=65/82;79%) showed better seizure control on the first AED than female patients (64/96;67%), However, this difference was not significant (p-value=0.06).

The study had limitations. The patients included were from a single centre in Glasgow which may limit the generalisability of the results. Furthermore, some data were not collected systematically in this study including those on pregnancy and mortality.

In conclusion, teenagers with different newly diagnosed epilepsies generally had good seizure control, better or comparable to the remission rate of the adult population. Moreover, patients with generalised epilepsy showed a better response to AED therapy than those with focal epilepsy. Additionally, patients showed different patterns of treatment outcome, which cannot be simply explained by seizure status at the last follow-up. The majority of teenagers with epilepsy were responsive to AED therapy. However, relapse was common and there was a high risk of seizure recurrence after treatment withdrawal. Most patients were controlled on monotherapy and on moderate drug doses. Furthermore, there was no significant difference in the efficacy rate among different AEDs. Overall, the poor tolerability rate in adolescents was 21%. Moreover, frequency and type of adverse effects varied among the different AEDs. As the efficacy of AEDs was comparable, tolerability is a key consideration in the selection of AEDs for this patient population

Disclosure of Conflicts of Interest

Zhibin Chen has received research grant from the University of Melbourne Early Career Researcher Grant Scheme. Patrick Kwan has received research grants from the National Health and Medical Research Council of Australia, the Australian Research Council, the US NIH, Hong Kong Research Grants Council, Innovation and Technology Fund, Health and Health Services Research Fund, and Health and Medical Research Fund. He/his institution also received speaker or consultancy fees and/or research grants from Eisai, GlaxoSmithKline, Johnson & Johnson, Pfizer, and UCB Pharma. Martin Brodie serves on the scientific advisory boards of Eisai, UCB Pharma, Lundbeck, GW Pharmaceuticals, and Takeda. He is on the speakers' bureau for Eisai, UCB Pharma, Lundbeck, Newbridge, Sanofi Aventis, and Abbott, and he has accepted travel grants for scientific meetings from Eisai, UCB Pharma, and Lundbeck. The remaining authors have no conflict of interest. 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. Comparison between doses of controlled and uncontrolled groups for each antiepileptic drug.

*Mann Whitney test was used. Key: **P≤0.01, ***P≤0.001.*

Table 1. Clinical characteristics of patients (total n=332)

		N (%)
Febrile convulsion		32 (10)
Birth trauma		7 (2)
Cerebral infection		4 (1)
Head injury		15 (5)
Cerebrovascular disease		13 (4)
Number of the pre-treatment seizure		
	1	18 (5)
	2	88 (27)
	3-5	97 (29)
	6-10	48 (15)
	11-20	17 (5)
	>20	64 (19)
Duration of the pre-treatment seizure (Months)		
	<2	52 (16)
	2-6	121 (36)
	7-12	42 (13)
	13-24	41 (12)
	25- 60	52 (16)
	>60	24 (7)
Psychiatric comorbidities		
	At baseline	17 (5)
	After treatment	43 (13)
Other medications at baseline or during follow-up		
	Medications for psychiatric disorders	30 (9)
	Oral contraceptive pills	6 (2)
	Other	22 (7)
Alcohol abuse at baseline or during follow-up		24 (4)
Recreational drug abuse at baseline or during follow-up		17 (5)
Seizure classification		

Absence with or without tonic-clonic seizures	12 (4)
Focal seizures	30 (9)
Focal /secondary generalised tonic-clonic seizures	75 (23)
Myoclonic with or without other seizure types	74 (22)
Secondary generalised tonic-clonic seizures	48 (14)
Tonic-clonic seizures	93 (28)
EEG classification	
Abnormal but not epileptiform	140 (42)
Epileptiform	108 (33)
Not performed	11 (3)
Normal*	73 (22)
MRI classification	
Epileptogenic	25 (7)
Not performed	133 (40)
Non-epileptogenic	29 (9)
Normal	145 (44)

**32 patients with focal epilepsy of unknown aetiology had normal EEG*

Table 2. Seizure-free rates of final antiepileptic drug monotherapies

Antiepileptic drug*	Seizure-free		
	Mixed cohort+	Generalised epilepsy+	Focal epilepsy+
Lamotrigine	75% (n=59/79)	79% (n=34/43)	69% (n=25/36)
Valproate	79% (n=57/72)	82% (n=45/55)	71% (n=12/17)
Carbamazepine	72% (n=26/36)	57% (n=4/7)	76% (n=22/29)
Levetiracetam	73% (n=22/30)	86% (n=19/22)	37% (n=3/8)
Oxcarbazepine	70% (n=7/10)	100% (2/2)	62% (n=5/8)
Topiramate	86% (n=6/7)	67% (n=2/3)	100% (n=4/4)

**other; tiagabine (n=4), lacosamide (n=4), gabapentin (n=1), zonisamide (n=1). +X^2 p-value was 0.92, 0.39 and 0.23 for mixed cohort, generalised and focal, respectively.*

Table 3. Tolerability rates of initial antiepileptic drug monotherapies and their dosages at adverse effects

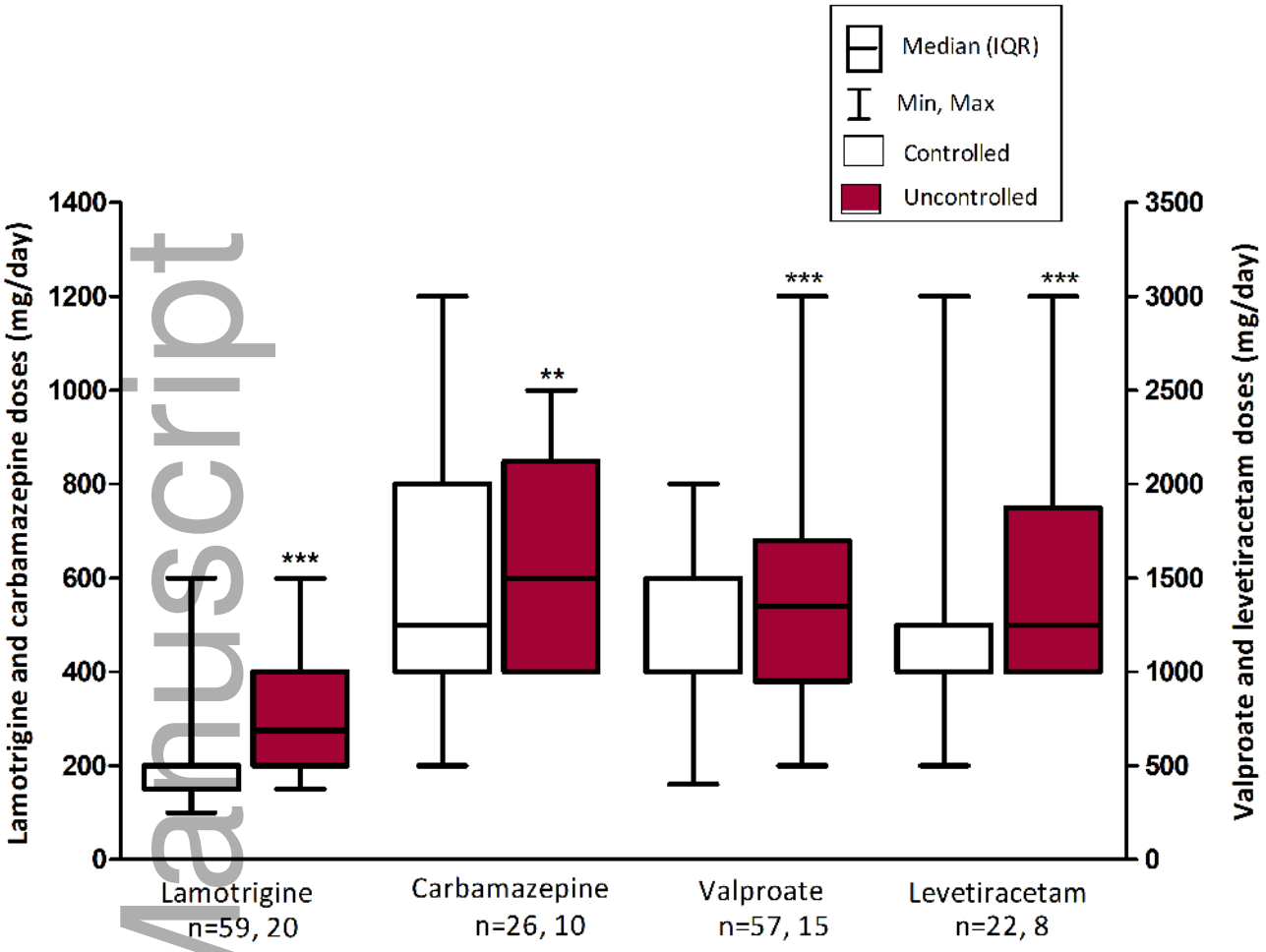
Antiepileptic drugs *	Intolerable adverse effect+	Dose in mg/day#
Lamotrigine	12% (n=15/124)	75 (25-350) [37.5-150]
Valproate	20% (n=16/81)	1000 (500-1800) [1000-1500]
Carbamazepine	26% (n=12/47)	400 (200-1000) [400-700]
Levetiracetam	38% (n=15/39)	1500 (750-4000) [1000-1750]
Oxcarbazepine	20% (n=2/10)	300, 750
Topiramate	56% (n=5/9)	100 (100-300) [100-100]
Tiagabine	22% (n=2/9)	20, 25

**other; felbamate (n=5), remacemide (n=5), gabapentine (n=3), mostly discontinued due to regulatory reasons. +X^2 P-value= 0.002. #*Dose at adverse effect median (range) [IQR], or dose of cases.

Table 4. Adverse drug reactions reported for individual antiepileptic drug

	LTG	VPA	CBZ	LEV	OXC	TPM	TGB	Other	Total
Psychiatric problems	4			15		3	1		23
Sedation	2	7	6	3	1		1		20
Rash	11		3	1	1				16
Cosmetic problems (weight changes, acne, hair problems)	1	9				2			12
Poor coordination/tremor		6	3	1			1		11
Headache	2		1						3
Insomnia				2				1	3
Gastrointestinal problems	1			1		1			3
Word finding difficulties/ poor concentration						2			2
Other		1	1			1		1	4
Total	21	23	14	23	2	9		5	97

Key; LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate, TGB: tiagabine.



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