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Prescription preferences of antiepileptic drugs in brain tumor patients: An international survey among EANO members

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Abstract

Background. This study aimed at investigating antiepileptic drug (AED) prescription preferences in patients with brain tumor-related epilepsy (BTRE) among the European neuro-oncology community, the considerations that play a role when initiating AED treatment, the organization of care, and practices with regard to AED withdrawal.

Methods. A digital survey containing 31 questions about prescription preferences of AEDs was set out among members of the European Association of Neuro-Oncology (EANO).

Results. A total of 198 respondents treating patients with BTRE participated of whom 179 completed the entire survey. Levetiracetam was the first choice in patients with BTRE for almost all respondents (90% [162/181]). Levetiracetam was considered the most effective AED in reducing seizure frequency (72% [131/181]) and having the least adverse effects (48% [87/181]). Common alternatives for levetiracetam as equivalent first choice included lacosamide (33% [59/181]), lamotrigine (22% [40/181]), and valproic acid (21% [38/181]). Most crucial factors to choose a specific AED were potential adverse effects (82% [148/181]) and interactions with antitumor treatments (76% [137/181]). In the majority of patients, neuro-oncologists were involved in the treatment of seizures (73% [132/181])). Other relevant findings were that a minority of respondents ever prescribe AEDs in brain tumor patients without epilepsy solely as prophylaxis (29% [53/181]), but a majority routinely considers complete AED withdrawal in BTRE patients who are seizure-free after antitumor treatment (79% [141/179]).

Conclusions. Our results show that among European professionals treating patients with BTRE levetiracetam is considered the first choice AED, with the presumed highest efficacy and least adverse effects.

Keywords

antiepileptic drug | brain neoplasms | levetiracetam | seizures | valproic acid

Seizures occur frequently in brain tumor patients and the incidence differs considerably between tumor entities. The seizure incidence is approximately 70%-80% in glioneuronal tumors, 60%-75% in low-grade gliomas, 25%-60% in high-grade gliomas, 20%-50% in meningiomas, and 20%-35% in brain metastases.[1] In case of a first seizure, there is a general consensus toward initiation of one of the newer non-enzyme-inducing antiepileptic drugs (non-EIAEDs), due to their generally good tolerability and limited drug-drug interactions.[2,3] Reducing the risk of

interactions with other drugs is of particular relevance for patients with brain tumor-related epilepsy (BTRE), as most patients receive systemic treatment and/or corticosteroids during the course of their disease.[4] With the increasing number of available non-EIAEDs over the past 20 years, the choice for an AED can be challenging.[5] There is a general lack of randomized controlled trials (RCTs) in BTRE to guide clinicians in their choice, causing variety in AED prescription preferences, between centers and countries.

Several surveys have been conducted focusing on the practice of AED prophylaxis in seizure-naïve brain tumor patients. Levetiracetam was the preferred AED in a survey among neurosurgeons mainly involved in brain tumors from the United States,[6] general neurosurgeons from the United Kingdom,[7] and Indian neuro-oncology professionals (mostly radiation oncologists),[8] while phenytoin was the preferred AED among general neurosurgeons from the United States,[9] Australia, and New Zealand.[10] Practice of prophylactic AED treatment during the perioperative period differed considerably between surveys, ranging from 25% to 78% of physicians prescribing prophylactic AED treatment in seizure-naïve brain tumor patients.[6–11] These surveys show clinical practice differences with regard to AED treatment in brain tumor patients between specialties and countries.

Currently, the AED prescription preferences of physicians treating patients with BTRE and which factors play a role when initiating or withdrawing AED treatment in these patients are unknown. The aim of this survey was to get insight into AED prescription preferences in patients with BTRE among the neuro-oncology community, the considerations that play a role when initiating AED treatment, the organization of care, and practices with regard to AED withdrawal in brain tumor patients with epilepsy.

Methods

A digital survey was set out via SurveyMonkey from June 15, 2020 until December 31, 2020 among members of the European Association of Neuro-Oncology (EANO) and national neuro-oncology working groups from the Netherlands, Germany, France, Italy, Switzerland, and Austria. The survey consisted of 5 parts, with a total of 31 questions. The five parts in the survey were as follows: (1) sociodemographic information, comprising 7 questions; (2) start of AED treatment, comprising 3 questions; (3) AED prescription preferences, comprising 10 questions; (4) organization of care, comprising 7 questions; and (5) AED withdrawal, comprising 4 questions. Only respondents ever prescribing AEDs to brain tumor patients for the treatment or prevention of seizures were allowed to continue with the second part of the survey. The complete survey can be found in the Supplementary Material. Participation was anonymous. Given this study had no potential for harm, this study was exempted from ethical review by our institutional review board.

Statistics

De-identified answers were exported directly from SurveyMonkey to SPSS software version 25.0 for analysis. Answers were reported as counts and relative proportions converted to percentages. The following analyses were done using the χ^2 to compare answers on questions of respondents with a surgical vs a nonsurgical profession and/or respondents working in an academic vs nonacademic hospital: (1) First choice AED in patients with BTRE; (2) AED interactions with antineoplastic treatment considered as a crucial factor for choosing an AED; (3) AEDs prescribed solely as prophylaxis in brain tumor patients without BTRE; (4) Professionals who treat patients with BTRE; (5) Presence of a specific care pathway; (6) Policy with regard to patients with pharmacoresistant BTRE; (7) Diagnostic tool used most frequently; (8) Routine use of electroencephalogram (EEG); (9) Tools used in daily clinical practice for monitoring patients with BTRE; (10) Monitoring AED drug levels; and (11) Routinely consideration of complete AED withdrawal in patients with BTRE who are seizure-free after antitumor treatment. A *P*-value of <.05 was considered statistically significant.

Results

Response Rate

A total of 217 professionals in neuro-oncology started the survey. Of these, 19 indicated to never prescribe AEDs to brain tumor patients for the treatment or prevention of seizures and were therefore excluded from further participation in the survey (Figure 1). Of all 198 respondents, 179 respondents completed the survey (2 respondents only finished part 1, 15 respondents only part 1 and 2, and 2 respondents only part 1 up to 4).

Sociodemographic Information

Demographic details of the 198 respondents who ever prescribed AEDs to brain tumor patients can be found in Table 1 and the profession of the respondents per country in Supplementary Table 1.

Start of AED Treatment

The vast majority of respondents prescribed AEDs in glioma (98% [192/196]), meningioma (85% [166/196]), and brain metastases (90% [177/196]) patients with epilepsy, while only a minority prescribed AEDs in patients with other brain tumors (14% [27/196]), such as primary central nervous system lymphoma. Respondents prescribed AEDs most often in glioma patients with epilepsy (84% [164/196]), followed by patients with brain metastases (12% [24/196]) and meningioma (4% [8/196]). A total of 86% (169/196) of the respondents always initiate AED treatment in brain tumor patients who had their first seizure, 11% (22/196) after multiple seizures, and 3% (5/196) only when the seizures interfere with the patient's daily life.

AED Prescription Preferences

For most respondents, levetiracetam is the first choice AED in general (90% [162/181]), both in mainly bilateral

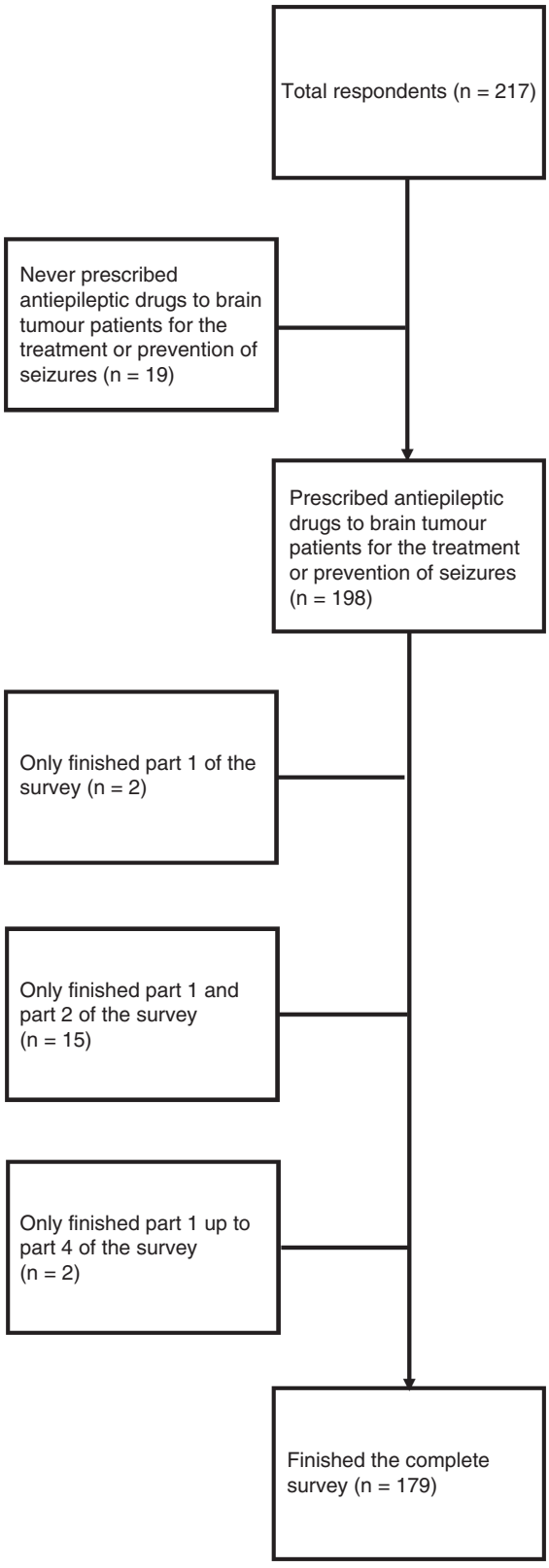


Figure 1. Flow chart of respondents.

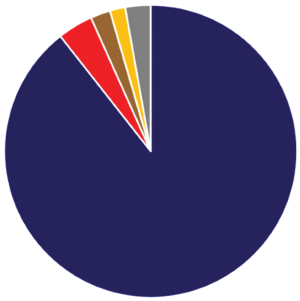
Table 1. Demographic Characteristics of Respondents of the Survey Prescribing Antiepileptic Drugs to Brain Tumor Patients for the Treatment or Prevention of Seizures

Characteristics	Number of Respondents (%)
Respondents	198 (100)
Age, years	
≤40	75 (38)
41-50	63 (32)
≥50	60 (30)
Sex	
Male	114 (58)
Female	81 (41)
Prefer not to say	3 (2)
Country of residence	
Austria	5 (3)
France	26 (13)
Germany	39 (20)
Italy	18 (9)
The Netherlands	30 (15)
Spain	12 (6)
Switzerland	20 (10)
United Kingdom	10 (5)
Other European countries	21 (11)
Non-European countries	17 (9)
Profession[1]	
Neuro-oncologist	81 (41)
Neurosurgeon	57 (29)
General neurologist	27 (14)
Medical oncologist	19 (10)
Radiation oncologist	13 (7)
Epileptologist	9 (5)
Other	6 (3)
Years of experience	
0-5	53 (27)
6-20	109 (55)
>20	36 (18)
Work settings[a]	
Municipal hospital	49 (25)
University hospital	146 (74)
Other	18 (9)

[a]Multiple options were possible, but the percentage is with regard to the 198 respondents, meaning the percentages do not add up to 100%.

tonic-clonic seizures (82% [148/181]) and in focal seizures (69% [125/181]). Levetiracetam is considered to have the least adverse effects in patients with BTRE according to 48% (87/181) of respondents (Figure 2). Lacosamide (33%

A



AED	LEV	LCM	PHT	LTG	Other
No. (%)	162 (90)	7 (4)	4 (2)	3 (2)	5 (3)

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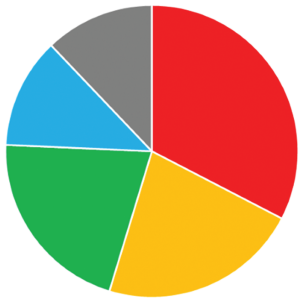

AED	LCM	LTG	VPA	No EFC	Other
No. (%)	59 (33)	40 (22)	38 (21)	22 (12)	22 (12)

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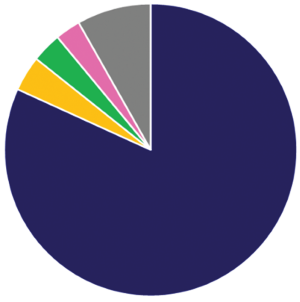
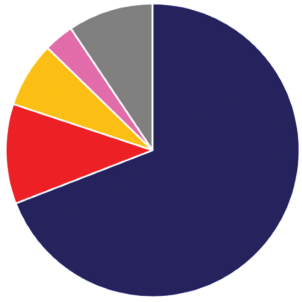


AED	LEV	LTG	VPA	CBZ	Other
No. (%)	148 (82)	7 (4)	6 (3)	5 (3)	15 (8)

D



AED	LEV	LCM	LTG	CBZ	Other
No. (%)	125 (69)	20 (11)	13 (7)	6 (3)	17 (9)

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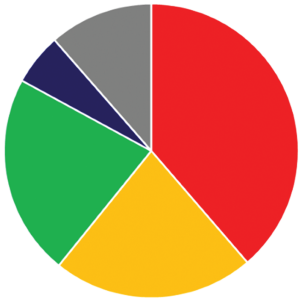

AED	LCM	LTG	VPA	LEV	Other
No. (%)	68 (38)	39 (22)	39 (22)	10 (6)	25 (14)

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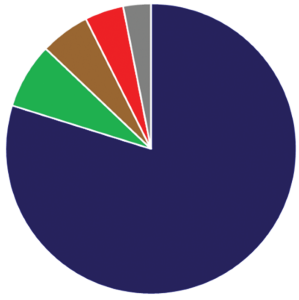

AED	LEV	VPA	PHT	LCM	Other
No. (%)	131 (72)	12 (7)	9 (5)	7 (4)	22 (12)

G

AED	LEV	LTG	LCM	BRV	Other
No. (%)	87 (48)	37 (20)	31 (17)	5 (3)	21 (12)

Antiepileptic drug	AED	Colour
Brivaracetam	BRV	
Carbamazepine	CBZ	
Lacosamide	LCM	
Lamotrigine	LTG	
Levetiracetam	LEV	
No equivalent first choice	No EFC	
Other	Other	
Phenytoin	PHT	
Valproic acid	VPA	

Figure 2. Antiepileptic drug prescription preferences: (A) First choice antiepileptic drug in general in brain tumor patients with epilepsy; (B) Equivalent first choice antiepileptic drug in brain tumor patients with epilepsy; (C) First choice antiepileptic drug in brain tumor patients with mainly bilateral tonic-clonic seizures; (D) First choice antiepileptic drug in brain tumor patients with mainly focal seizures; (E) Antiepileptic drug of choice when first antiepileptic drug has failed due to adverse effects or inefficacy in brain tumor patients with epilepsy; (F) Antiepileptic drug most effective in reducing seizure frequency in brain tumor patients with epilepsy; (G) Antiepileptic drug with least adverse effects in brain tumor patients with epilepsy.

[59/181] and 38% [68/181]), lamotrigine (22% [40/181] and 22% [39/181]), and valproic acid (21% [38/181] and 22% [39/181]) were believed to be an equivalent first choice and AED of choice when the first AED has failed in patients with BTRE. Levetiracetam was considered the first choice AED in patients with BTRE by respondents from all participating countries, but with regard to the equivalent first choice AED countries differed considerably (Table 2). Most crucial factors according to the respondents in the choice of a specific AED for patients with BTRE included potential adverse effects (82% [148/181]), interactions with antineoplastic treatments (76% [137/181]), interactions with other drugs (54% [97/181]), expected efficacy (53% [96/181]), seizure type (39% [71/181]), comorbidities (31% [56/181]), age (28% [51/181]), gender (17% [31/181]), patient's preference (12% [21/181]), stage of the disease (11% [20/181]), being routine practice (11% [20/181]), type of brain tumor (8% [15/181]), possible impact on overall survival (7% [12/181]), insurance coverage (6% [11/181]), or other reasons (4% [7/181]) such as option of intravenous use. The majority of the respondents (59% [106/181]) have not experienced that they could not prescribe the preferred AED, while this has been an issue in 19% (35/181) due to patient objection, in 9% (17/181) due to comorbidities, in 9% (18/181) due to unavailability, in 6% (10/181) due to no coverage by insurance, and in 2% (3/181) for other reasons. Of the respondents, 71% (128/181) do not prescribe AEDs in seizure-free brain tumor patients for prophylaxis, while 17% (30/181) sometimes prescribe AEDs as perioperative prophylaxis, 6% always as perioperative prophylaxis, 5% (9/181) sometimes for prophylaxis during the course of the disease, 1% (2/181) always during the course of the disease, and 1% (2/181) sometimes for prophylaxis during the end-of-life phase. Countries varied considerably with regard to AED prophylactic practices (Table 3).

AED prescription preferences were compared between respondents with a surgical and nonsurgical profession, and several differences were found. Interaction with antineoplastic treatment was seen as the most important factor when choosing an AED in patients with BTRE by 53% (27/51) of the respondents with a surgical profession vs 85% (110/130, $P < .001$) with a nonsurgical profession. Non-EIAEDs as first choice in patients with BTRE were highly preferred by both respondents with a surgical (94% [48/51]) vs a nonsurgical profession (98% [128/130], $P = .109$). However, with regard to the consideration of an equivalent AED first choice in patients with BTRE, respondents with a surgical profession (88% [45/51]) chose significantly less often non-EIAEDs compared to respondents with a nonsurgical profession (96% [125/130], $P = .045$). All respondents that prescribe AEDs most often in patients with meningioma and in brain metastases typically chose non-EIAEDs as equivalent first choice, while this was 93% (139/150) in glioma. A significantly higher percentage of the respondents with a surgical profession (41% [21/51]) ever prescribed AEDs solely as prophylaxis in brain tumor patients without epilepsy vs a nonsurgical profession (25% [32/130], $P = .028$). No significant differences were found between professionals working in an academic vs a nonacademic hospital with regard to considering interaction with antineoplastic treatment as the most crucial factor when choosing an AED (76% [100/132] vs 76% [37/49],

Table 3. Ever Prescribe Antiepileptic Drugs in Brain Tumor Patients Without Epilepsy, Solely as Prophylaxis, per Country

Country	Antiepileptic Drugs Solely as Prophylaxis	
	No	Yes
Austria, no. (%)	2 (50)	2 (50)
France, no. (%)	14 (61)	9 (39)
Germany, no. (%)	33 (89)	4 (11)
Italy, no. (%)	8 (50)	8 (50)
The Netherlands, no. (%)	24 (86)	4 (14)
Spain, no. (%)	5 (45)	6 (55)
Switzerland, no. (%)	19 (100)	0 (0)
United Kingdom, no. (%)	5 (56)	4 (44)
Other European countries, no. (%)	12 (63)	7 (37)
Non-European countries, no. (%)	6 (40)	9 (60)

Table 2. Most Frequently Chosen Equivalent First Choice Antiepileptic Drug in Patients With Brain Tumor-Related Epilepsy per Country

Country	Antiepileptic Drugs				
	Lacosamide	Lamotrigine	Valproic Acid	No Equivalent First Choice	Other
Austria, no. (%)	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)
France, no. (%)	12 (52)	8 (35)	0 (0)	1 (4)	2 (9)
Germany, no. (%)	13 (35)	12 (42)	2 (5)	7 (19)	3 (8)
Italy, no. (%)	9 (56)	3 (19)	0 (0)	0 (0)	4 (25)
The Netherlands, no. (%)	2 (7)	3 (11)	21 (75)	0 (0)	2 (7)
Spain, no. (%)	6 (55)	0 (0)	4 (36)	1 (9)	0 (0)
Switzerland, no. (%)	7 (37)	6 (32)	1 (5)	3 (16)	2 (11)
United Kingdom, no. (%)	0 (0)	4 (44)	1 (11)	4 (44)	0 (0)
Other European countries, no. (%)	5 (26)	2 (11)	4 (21)	3 (16)	5 (26)
Non-European countries, no. (%)	1 (7)	2 (13)	5 (33)	3 (20)	4 (27)

P = .972), non-EIAEDs as first choice AED in general (97% [128/132] vs 98% [48/49], *P* = .718), non-EIAEDs as equivalent first choice AED (95% [125/132] vs 92% [45/49], *P* = .474), or ever prescribed AEDs solely as prophylaxis in seizure-naïve patients (30% [40/132] vs 27% [13/49], *P* = .620).

Organization of Care

Of all specialists treating brain tumor patients with epilepsy, neuro-oncologists were most frequently involved (73% [132/181]), followed by neurosurgeons (44% [79/181]), general neurologists (43% [77/181]), epileptologists (38% [69/181]), radiation oncologists (20% [37/181]), and medical oncologists (17% [31/181]). Most institutes (71% [129/181]) do not have a specific care pathway for brain tumor patients with epilepsy. In institutes who do have a specific care pathway (29% [52/181]), this pathway consists of care/consultation by a neuro-oncologist (23% [12/52]), epileptologist (19% [10/52]), neurologist (15% [8/52]), other (12% [6/52]), or was not specified (25% [13/52]). Brain tumor patients with pharmacoresistant epilepsy are treated by the respondents themselves in 29% (58/181), while 59% (106/181) refers these patients to an expert within their institute, and 23% (42/181) refers these patients to an expert outside their institute. The most frequently used tools to diagnose epilepsy were: a patients' history and/or witness account (84% [152/181]), EEG (16% [29/181]), but video event recording was never used (0% [0/181]). EEG is routinely used for diagnostic purposes by 42% (76/181) of the respondents. To monitor a patient with BTRE, 50% (91/181) of the respondents use clinical history plus a seizure diary, 38% (69/181) clinical history only, 10% (19/181) clinical history plus a seizure diary plus neurocognitive testing, and 1% (2/181) other tools. AED drug levels during follow-up of patients with BTRE are not monitored by 13% (24/181) of the respondents, 43% (77/181) rarely, 29% (52/181) sometimes, 10% (18/181) often, and 6% (10/181) always.

BTRE is significantly more often treated in academic vs nonacademic centers by neuro-oncologists (77% [102/132] vs 61% [30/49], *P* = .031), epileptologists (45% [59/132] vs 20% [10/49], *P* = .003), neurosurgeons (48% [62/132] vs 31% [15/49], *P* = .031), and radiation oncologists (24% [32/132] vs 10% [5/49], *P* = .037), but not medical oncologists (19% [25/132] vs 12% [6/49], *P* = .288), and the opposite for general neurologists (36% [48/132] vs 59% [29/49], *P* = .006). In academic vs nonacademic centers patients with pharmacoresistant BTRE are significantly more often referred to an expert within the institute (64% [85/132] vs 43% [21/49], *P* = .009) and less often to an expert outside the institute (17% [23/132] vs 39% [19/49], *P* = .002). No significant differences were found between professionals working in an academic vs a nonacademic hospital with regard to having a specific care pathway, diagnostic tools, and tools used for monitoring BTRE patients (data not shown).

AED Withdrawal

Almost all respondents ever considered to reduce the number of AEDs (93% [167/179]) or reduce the AED dose (93% [166/179]) in patients with BTRE who were seizure-free after antitumor treatment. A majority of the respondents (79% [142/179]) routinely consider complete AED withdrawal in patients with BTRE who are seizure-free after antitumor treatment. If considered, this was most often in meningioma (72% [129/179]), followed by low-grade glioma (47% [85/179]), solitary brain metastasis (41% [74/179]), high-grade glioma (30% [53/179]), other brain tumor entities (17% [30/179]), and the least in patients with multiple brain metastases (16% [28/179]). Crucial factors when determining whether or not patients are suitable for AED withdrawal included period of seizure freedom (94% [169/179]), presumed risk of seizure relapse (65% [116/179]), tumor type (63% [113/179]), AED adverse effects (59% [106/179]), patient preference (57% [102/179]), seizure severity (54% [96/179]), completeness of tumor resection (49% [87/179]), driving restrictions (37% [67/179]), time since last antitumor treatment (36% [64/179]), long-term toxicity of AEDs (22% [40/179]), distress of taking daily medication (13% [23/179]), or other factors (4% [7/179]) such as characteristics of the EEG.

A significantly higher percentage of neurosurgeons (98%, [49/50]) routinely consider complete AED withdrawal in patients with BTRE who are seizure-free after antitumor treatment compared to respondents with a nonsurgical profession (72% [93/129], *P* < .001), while no significant difference was found between respondents working in an academic (81% [105/130]) vs nonacademic hospital (76% [37/49], *P* = .438).

Discussion

The aim of this survey largely conducted in Western Europe was to gain more insight into AED prescription preferences among the neuro-oncology community and the considerations which play a role when initiating AED treatment in brain tumor patients. Levetiracetam was the first choice in patients with BTRE for almost all respondents. Commonly chosen alternatives to levetiracetam as equivalent first choice or when patients had experienced treatment failure on their first choice AED due to inefficacy or intolerable adverse effects included lacosamide (preferred in Austria, France, Italy, Spain, and Switzerland), lamotrigine (preferred in Germany and the United Kingdom), and valproic acid (preferred in the Netherlands). Lacosamide and lamotrigine showed similar effectiveness in diffuse gliomas in a recent retrospective observational study,[12] but high-quality comparative AED second-line studies in BTRE are currently lacking and these country-specific differences most probably reflect differing expert opinion per country and invites to conduct a comparative European randomized second-line AED study in BTRE.[13]

It is in line with expectations that levetiracetam is considered the first choice AED among the majority of respondents. It is the most studied AED in the brain tumor population, recommended by the EANO guidelines as a preferred first choice (together with lamotrigine), with good efficacy, a favorable adverse effect profile, and no interactions with antitumor treatments.[13,14] Although caution is advised with regard to psychiatric adverse effects, the most common adverse effects leading to discontinuation of levetiracetam.[15] When considering to start an AED, its supposed adverse effect profile and potential interactions with antitumor agents

appear to be of greater importance to physicians than AED efficacy. It seems likely that these factors have contributed substantially in making levetiracetam so well-accepted. In previous surveys on prophylactic AED use, levetiracetam was also identified as the preferred AED.[6–8] The same applies to equivalent first choices lacosamide and lamotrigine, which have no interactions with antitumor treatments and are generally seen as having a favorable adverse effect profile.[2] Valproic acid was another AED considered by respondents as an equivalent first choice, despite being an enzyme-inhibiting AED and commonly considered to have a less favorable adverse effect profile as the former mentioned AEDs,[2] although the latter is disputed.[15,16] Based on the factors considered important when initiating an AED it is not surprising that older EIAEDs, such as phenobarbital and phenytoin, were rarely favored. While the interest for lacosamide in BTRE has increased in the past years,[13,17–23] this does not apply to lamotrigine.[13,24,25]

We did find some differences in AED prescription preferences between respondents with a surgical vs nonsurgical profession. Neurosurgeons seem to take interactions with antineoplastic treatment less into consideration than respondents with a nonsurgical profession. While this does not translate in a difference in initiating EIAEDs as a first choice in patients with BTRE, neurosurgeons do consider EIAEDs significantly more often as an equivalent first choice than respondents with a nonsurgical profession. This difference might be explained by the efficacy of phenytoin as perioperative AED prophylaxis as shown in a meta-analysis of 4 RCTs,[26] and that potential interactions of AEDs with antineoplastic agents are not an urgent issue in the perioperative stage of the disease trajectory. The guidelines on the treatment of BTRE discourages initiating EIAEDs in brain tumor patients.[14] Despite the differences in AED preference between surgical and nonsurgical respondents, in line with the guidelines the vast majority of respondents generally avoid initiating EIAEDs in patients with BTRE.[14,27,28] Similarly, the majority of respondents always initiate AEDs in brain tumor patients after a first seizure has occurred and never prescribe AEDs solely as prophylaxis in brain tumor patients without epilepsy, which is in line with current guidelines on the treatment of both low-grade and high-grade glioma patients,[14,27–29] yet this topic is highly debated.[30] According to a Cochrane systematic review, there is insufficient evidence to allow recommendations on prophylactic peri-operative AED treatment in brain tumor patients.[31,32] Only 29% of the survey respondents ever prescribe AEDs to brain tumor patients without epilepsy, solely as prophylaxis, but results differed between countries in the survey and ranged from 0% (Switzerland) to 60% (non-European countries). This wide range corresponds to results from surveys conducted in other countries, which showed considerable differences as well. In a survey among neurosurgeons from Australia and New Zealand, only 25% of respondents reported to prescribe AEDs solely as prophylaxis,[10] while this was 70%-78% of respondents in surveys among neuro-oncology professionals from Asia and North America.[6,8,11] Currently a phase III RCT is being conducted comparing prophylactic levetiracetam vs no AED before surgery,[33] which hopefully will guide neuro-oncology professionals worldwide in making evidence-based decisions in clinical practice.

In line with expectations, the organization of care does seem to differ between academic and nonacademic centers. In academic centers more specialist professionals (eg, neuro-oncologists) treat patients with BTRE and if BTRE patients show pharmacoresistant epilepsy, these patients are more often referred to an expert within the institute instead of outside the institute. Most respondents routinely consider complete AED withdrawal in patients with BTRE, who are seizure-free after antitumor treatment, especially in meningioma patients, who have become seizure-free after antitumor treatment. Again, a difference was found between surgical vs nonsurgical professionals, the first significantly more often considering complete AED withdrawal. This might be explained by a different patient population seen by neurosurgeons, in which the antitumor treatment comprises tumor resection only, such as meningioma patients. A few studies have been conducted with regard to AED withdrawal in BTRE patients. A prospective study in glioma patients showed that about a quarter (12/46) of low-grade and anaplastic glioma patients with epilepsy and at least 1-year seizure freedom after the last antitumor treatment had a recurrent seizure within 1.5 years after AED withdrawal compared to 8% (2/25) of patients continuing AED treatment.[34] In retrospective AED withdrawal studies in brain tumor patients with a history of seizures similar recurrent seizure rates were reported: 19% (3/16) in adult patients (median follow-up 3.1 years)[35] and 27% (17/62) in pediatric patients (median follow-up 2.3 years).[36] These studies show that AED withdrawal was accompanied by a considerable risk of recurrent seizures. Therefore, AED withdrawal needs to be considered carefully, and the clinical decision to withdraw AEDs should preferably be based on shared decision making.[37,38] According to the survey participants, the most crucial factor to consider when determining suitability for AED withdrawal in brain tumor patients is the period of seizure freedom. To date, no studies have been conducted with regard to the optimal period of seizure freedom to withdraw AEDs in patients with BTRE, and this remains to be elucidated to help clinicians and patients guide in this difficult decision.

The survey has only been distributed to members of the EANO and several national European working groups, with less than 10% of respondents from non-European countries. Furthermore, the group of respondents are not always the physicians who initiate AED treatment in this population and anyone inclined to respond may reflect a unique practice pattern, hampering generalizability of the results. The survey was disseminated via different channels, such as the EANO newsletter and various national neuro-oncology working groups, as a result of which we were not able to determine the response rate. Mainly because of practical reasons, the questions were not repeated for each brain tumor entity separately (glioma, brain metastases, and meningioma). Therefore, a clear distinction between brain tumor entities cannot be made, and prescription preferences might differ between these subgroups. However, given the general preference for levetiracetam, it could be expected that levetiracetam is the first choice AED across all brain tumor entities. It seems most likely that the number of respondents prescribing AEDs to specific groups of brain tumor patients with epilepsy not only reflects the frequency at which respondents

see patients with these tumor types, but also the likelihood of the tumor type presenting with epilepsy. As a result, it cannot be derived from this question what percentage of respondents would prescribe AEDs if they would encounter a patient with a certain type of brain tumor (eg, a central nervous system lymphoma) and epilepsy. Although we gained information on crucial factors in choosing an AED for brain tumor patients with epilepsy, we do not know why the respondents consider levetiracetam as most effective AED with the least adverse effects. This could be based on AED studies conducted in brain tumor patients, RCTs in general epilepsy patients, clinical experience, or other sources of information. Given the lack of high-quality comparative efficacy/effectiveness studies in the brain tumor population, it would be interesting to know which sources of information informed the respondents.

In conclusion, our results suggest levetiracetam is considered the first choice AED in brain tumor patients with epilepsy and believed to have the highest efficacy and least adverse effects, by the vast majority of European neuro-oncology professionals treating patients with BTRE. Most crucial factors to choose an AED are potential adverse effects and interactions with antitumor treatments and other drugs. This is supported by the finding that non-EIAEDs are favored by a large majority of respondents. Commonly chosen alternatives to levetiracetam were lacosamide, lamotrigine, and valproic acid. EANO guidelines seem to be followed by the majority of EANO members on topics such as (un)favored AEDs. The results of this survey are a representative reflection of best practices among experts in the field of neuro-oncology and may help to inform all professionals treating patients with BTRE.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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