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## Optimizing antiseizure medication treatment in glioma patients with epilepsy

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## **PART III**

Antiseizure medication prescription behavior  
and treatment policy



## CHAPTER 9

### 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.

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### Keywords

Brain neoplasms, valproic acid, levetiracetam, antiepileptic drug, seizures

## Introduction

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.<sup>1</sup> In case of a first seizure, there is a general consensus towards initiation of one of the newer non-enzyme-inducing antiepileptic drugs (non-EIAEDs), due to their generally good tolerability and limited drug-drug interactions.<sup>2</sup> 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.<sup>4</sup> With the increasing number of available (non-EI)AEDs over the past twenty years, the choice for an AED can be challenging.<sup>5</sup> 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 of America (USA),<sup>6</sup> general neurosurgeons from the United Kingdom,<sup>7</sup> and Indian neuro-oncology professionals (mostly radiation oncologists),<sup>8</sup> while phenytoin was the preferred AED among general neurosurgeons from the USA,<sup>9</sup> Australia, and New Zealand.<sup>10</sup> Practice of prophylactic AED treatment during the perioperative period differed considerably between surveys, ranging from 25-78% of physicians prescribing prophylactic AED treatment in seizure-naïve brain tumor patients.<sup>6-11</sup> 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. 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 15-06-2020 until 31-12-2020 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 five parts, with a total of 31 questions. The five parts in the

survey were as follows: 1) sociodemographic information, comprising seven questions; 2) start of AED treatment, comprising three questions; 3) AED prescription preferences, comprising ten questions; 4) organization of care, comprising seven questions; and 5) AED withdrawal, comprising four 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. 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  $\chi^2$  to compare answers on questions of respondents with a surgical versus a non-surgical profession and/or respondents working in an academic versus non-academic hospital: 1) First choice AED in patients with BTRE; 2) AED interactions with antineoplastic treatment considered as 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 pharmaco-resistant 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  $<0.05$  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 one, 15 respondents only part one and two, and 2 respondents only part one up to four).

### **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.



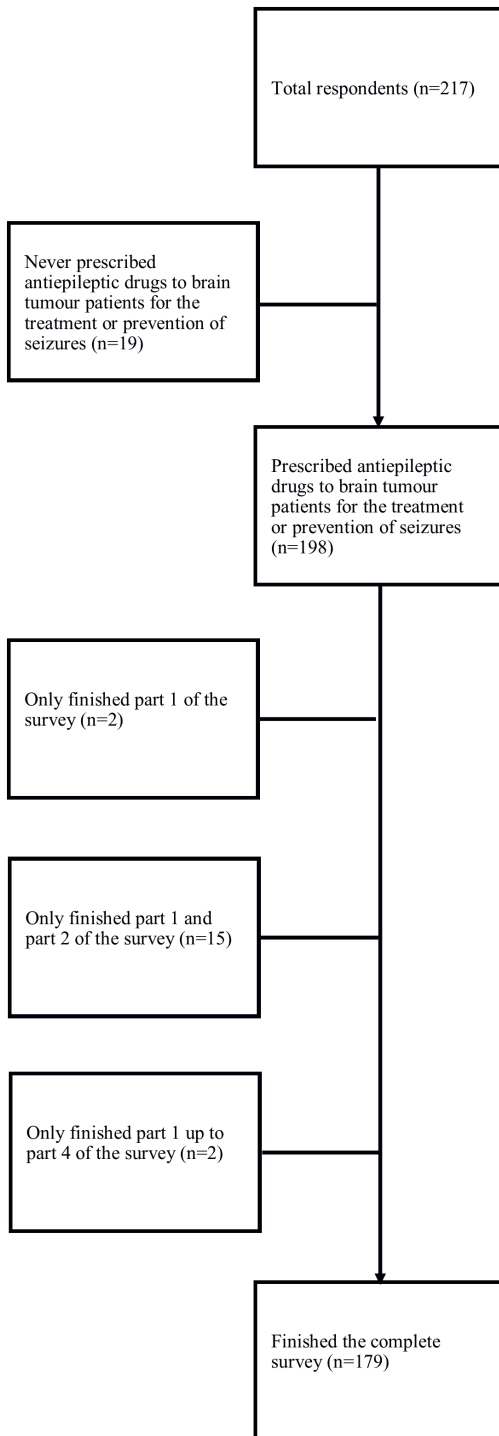


Figure 1. Flow-chart of respondents.

**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	
≤40 years	75 (38)
41-50 years	63 (32)
≥50 years	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 <sup>1</sup>	
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 years	53 (27)
6-20 years	109 (55)
>20 years	36 (18)
Work setting <sup>1</sup>	
Municipal hospital	49 (25)
University hospital	146 (74)
Other	18 (9)

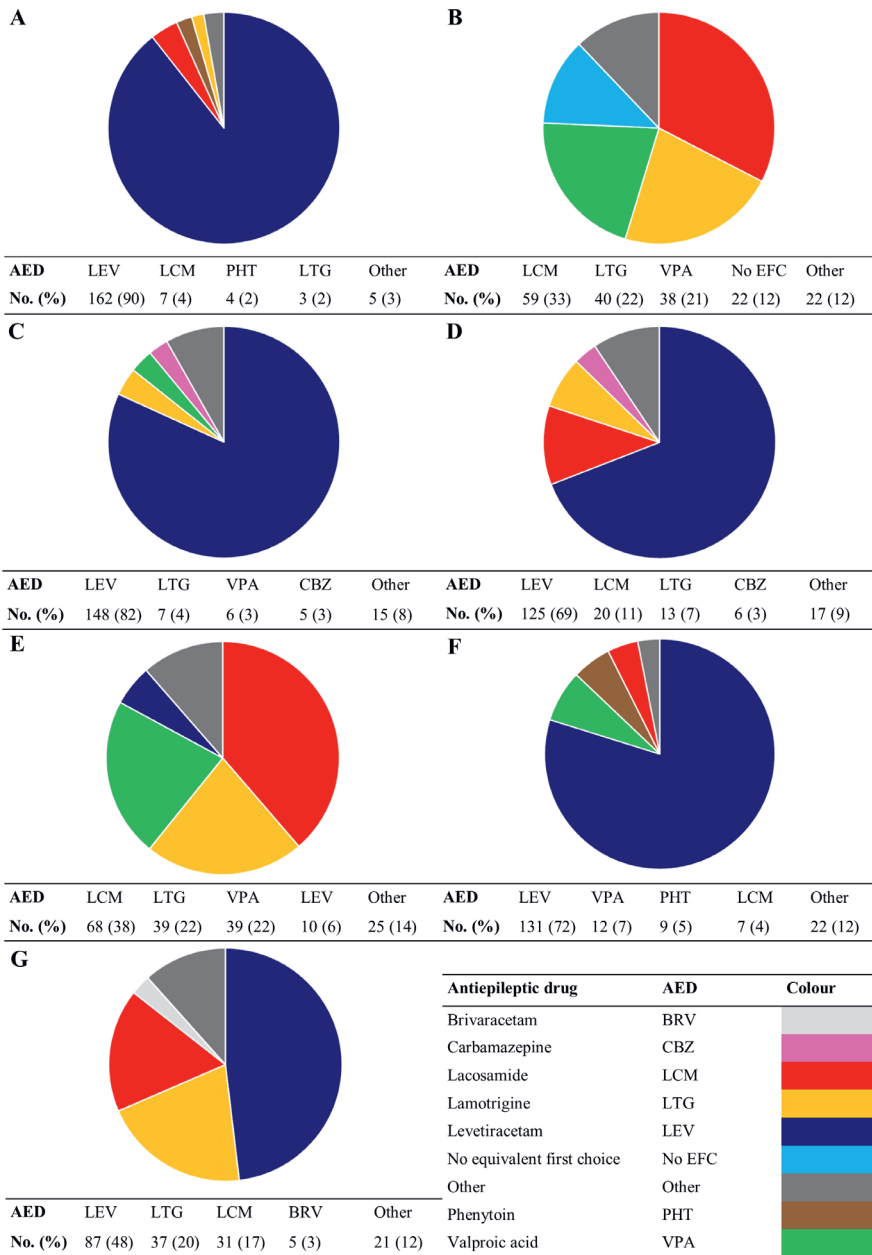
<sup>1</sup>Multiple options were possible, but the percentage is with regard to the 198 respondents, meaning the percentages do not add up to 100%

### 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 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% [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).



**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.

**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)

AED prescription preferences were compared between respondents with a surgical and non-surgical 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 versus 85% (110/130,  $p < 0.001$ ) with a non-surgical profession. Non-EIAEDs as first choice in patients with BTRE were highly preferred by both respondents with a surgical (94% [48/51]) versus a non-surgical profession (98% [128/130],  $p = 0.109$ ). 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 non-surgical profession (96% [125/130],  $p = 0.045$ ). 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 versus a non-surgical profession (25% [32/130],  $p = 0.028$ ). No significant differences were found between professionals working in an academic versus a non-academic hospital with regard to considering interaction with antineoplastic treatment as the most crucial factor when choosing an AED (76% [100/132] versus 76% [37/49],  $p = 0.972$ ), non-EIAEDs as first choice AED in general (97% [128/132] versus 98% [48/49],  $p = 0.718$ ), non-EIAEDs as equivalent first choice AED (95% [125/132] versus 92% [45/49],  $p = 0.474$ ), or ever prescribed AEDs solely as prophylaxis in seizure-naïve patients (30% [40/132] versus 27% [13/49],  $p = 0.620$ ).

**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)

### 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]), electroencephalogram (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 versus non-academic centers by neuro-oncologists (77% [102/132] versus 61% [30/49],  $p=0.031$ ), epileptologists (45%

[59/132] versus 20% [10/49],  $p=0.003$ ), neurosurgeons (48% [62/132] versus 31% [15/49],  $p=0.031$ ), and radiation oncologists (24% [32/132] versus 10% [5/49],  $p=0.037$ ), but not medical oncologists (19% [25/132] versus 12% [6/49],  $p=0.288$ ), and the opposite for general neurologists (36% [48/132] versus 59% [29/49],  $p=0.006$ ). In academic versus non-academic centers patients with pharmacoresistant BTRE are significantly more often referred to an expert within the institute (64% [85/132] versus 43% [21/49],  $p=0.009$ ) and less often to an expert outside the institute (17% [23/132] versus 39% [19/49],  $p=0.002$ ). No significant differences were found between professionals working in an academic versus a non-academic 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 non-surgical profession (72% [93/129],  $p<0.001$ ), while no significant difference was found between respondents working in an academic (81% [105/130]) versus non-academic hospital (76% [37/49],  $p=0.438$ ).

## **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,<sup>12</sup> 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.<sup>13</sup>

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.<sup>13, 14</sup> Although caution is advised with regard to psychiatric adverse effects, the most common adverse effects leading to discontinuation of levetiracetam.<sup>15</sup> 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.<sup>6-8</sup> 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.<sup>2</sup> 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,<sup>2</sup> although the latter is disputed.<sup>15, 16</sup> 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,<sup>13, 17-23</sup> this does not apply to lamotrigine.<sup>13, 24, 25</sup>

We did find some differences in AED prescription preferences between respondents with a surgical versus non-surgical profession. Neurosurgeons seem to take interactions with antineoplastic treatment less into consideration than respondents with a non-surgical 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 non-surgical profession. This difference might be explained by the efficacy of phenytoin as perioperative AED prophylaxis as shown in a meta-analysis of four RCTs,<sup>26</sup> 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.<sup>14</sup> Despite the differences in AED preference between surgical and non-surgical respondents, in line with the guidelines the vast majority of respondents generally avoid initiating EIAEDs in patients with BTRE.<sup>14, 27, 28</sup> 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,<sup>14, 27-29</sup> yet this topic is highly debated.<sup>30</sup> According to a Cochrane systematic review, there is insufficient evidence to allow recommendations on prophylactic peri-operative AED treatment in brain tumor patients.<sup>31, 32</sup> 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,<sup>10</sup> while this was 70-78% of respondents in surveys among neuro-oncology professionals from Asia and North-America.<sup>6, 8, 11</sup> Currently a phase III RCT is being conducted comparing prophylactic levetiracetam versus no AED before surgery,<sup>33</sup> 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 non-academic centers with regard to more specialist professionals (e.g. neuro-oncologists) treat patients with BTRE in academic centers and if BTRE patients show pharmaco-resistant epilepsy, they are more often referred to an expert within the institute instead of outside the institute in academic centers. 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 versus non-surgical 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 one 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.<sup>34</sup> 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)<sup>35</sup> and 27% (17/62) in paediatric patients (median follow-up 2.3 years).<sup>36</sup> 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.<sup>37,38</sup> 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 (e.g. 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)

avored 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.

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### **Authorship**

LD, MJvdB, JAFK, and RR designed the study. PBvdM performed data-analysis with input from LD, JAFK, RR, and MJvdB. PBvdM wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the paper, and approved the final version. PBvdM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### **Additional contributions**

We acknowledge the contribution of EANO and national neuro-oncology working groups of the Netherlands (Dutch Neuro-Oncology Society), Germany (Neurooncology Working Group of the German Cancer Society), France (Association des Neuro-Oncologues d'Expression Francaise), Switzerland (Swiss Neuro-Oncology Society), Italy (Italian Association of Neuro-Oncology), and Austria (Society of Austrian Neurooncology) for distributing the survey among their members.

### **Conflict of interest statement**

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, AdastrA. The following for-profit companies have supported clinical trials and contracted research conducted by MP with payments made to his institution: Böhrlinger-Ingelheim, Bristol-Myers Squibb, Roche, Daiichi Sankyo, Merck Sharp & Dome, Novocure, GlaxoSmithKline, AbbVie.

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## Supplementary material

**Supplementary Table 1.** Profession of the respondents per country.

Country	Profession				
	Neuro-oncologist	General neurologist/ Epileptologist	Neurosurgeon	Medical/ Radiation oncologist	Other
Austria, no. (%)	3 (60)	1 (20)	1 (20)	0 (0)	0 (0)
France, no. (%)	14 (54)	2 (8)	7 (27)	3 (12)	0 (0)
Germany, no. (%)	11 (28)	5 (13)	20 (51)	3 (8)	0 (0)
Italy, no. (%)	5 (28)	7 (39)	4 (22)	2 (11)	0 (0)
The Netherlands, no. (%)	19 (63)	4 (13)	5 (17)	1 (3)	1 (3)
Spain, no. (%)	2 (17)	1 (8)	0 (0)	7 (58)	2 (17)
Switzerland, no. (%)	9 (45)	1 (5)	5 (25)	5 (25)	0 (0)
United Kingdom, no. (%)	2 (20)	2 (20)	2 (20)	3 (30)	1 (10)
Other European countries, no. (%)	4 (19)	4 (19)	9 (43)	4 (19)	0 (0)
Non-European countries, no. (%)	8 (47)	2 (12)	4 (24)	3 (18)	0 (0)

The digital survey consisting of five parts, with a total of 31 questions

**Part 1) Sociodemographic information**

- Age in years?
- Gender?
  - Male
  - Female
  - Prefer not to say
  - Other (please specify)
- Country of residence? \_\_\_\_\_
- Profession? Multiple options possible
  - Medical Oncologist
  - General Neurologist
  - Neuro-oncologist
  - Epileptologist
  - Radiation Oncologist
  - Neurosurgeon
  - Nurse specialist Neuro-Oncology
  - Other, i.e.: \_\_\_\_\_
- Years of experience in Neuro-Oncology practice?
  - 0-1 year
  - 2-5 years
  - 6-20 years
  - more than 20 years
- Work setting? Multiple options possible
  - Municipal hospital
  - University hospital
  - Other, i.e.: \_\_\_\_\_
- Do you ever prescribe AEDs to brain tumor patients for the treatment or prevention of seizures?
  - Yes (continue with part #2)
  - No (end of questionnaire)

**Part 2) Start of AED treatment**

- In which group of brain tumor patients with epilepsy do you prescribe AEDs? Multiple options possible
  - Glioma
  - Meningioma
  - Brain metastases
  - Other, i.e.
- In which group of brain tumor patients with epilepsy do you most commonly prescribe AEDs? Choose one option
  - Glioma
  - Meningioma
  - Brain metastases
  - Other, i.e.

- When would you consider initiating AED treatment in patients with a brain tumor who have had at least one seizure? Choose one option
  - Always after the first seizure
  - After multiple seizures
  - Only when seizures are interfering with the patient's daily life (e.g. tonic-clonic seizures or daily focal seizures)

### **Part 3) AED prescription preferences**

- Which AED is in general **your** first choice in patients with a brain tumor having epilepsy? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e.		
- Is there another AED that **you** consider an equivalent first choice in patients with a brain tumor having epilepsy? Choose one option.
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> No equivalent first choice		
<input type="checkbox"/> Other, i.e.		
- Which AED is **your** first choice in brain tumor patients mainly having bilateral tonic-clonic seizures? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e.		
- Which AED is **your** first choice in brain tumor patients mainly having focal seizures? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e.		



- Which factors are **according to you** most crucial when you have to choose an AED for patients with brain tumor-related epilepsy? Multiple options possible
  - Interactions with other drugs (other than antineoplastic treatment)
  - Interactions with antineoplastic treatment (radio-, chemo-, immuno- or targeted therapy)
  - Gender  Age
  - Seizure type  Type of brain tumor
  - Expected efficacy of AED  Comorbidity
  - Potential adverse effects  Patient's preferences
  - Stage of the disease  Insurance coverage
  - Being routine practice  Potential effect on overall survival
  - Other, i.e. \_\_\_\_\_
  
- Which AED is generally **your** choice when the first AED has failed due to adverse effects or inefficacy? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e. _____		
  
- Which AED **do you believe** is most effective in reducing seizure frequency in brain-tumor related epilepsy? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e. _____		
  
- Which AED **do you believe** has the least adverse effects in the treatment of brain-tumor related epilepsy? Choose one option
 

<input type="checkbox"/> Brivaracetam	<input type="checkbox"/> Lamotrigine	<input type="checkbox"/> Primidone
<input type="checkbox"/> Carbamazepine	<input type="checkbox"/> Levetiracetam	<input type="checkbox"/> Sodium valproate
<input type="checkbox"/> Clobazam	<input type="checkbox"/> Oxcarbazepine	<input type="checkbox"/> Tiagabine
<input type="checkbox"/> Clonazepam	<input type="checkbox"/> Perampanel	<input type="checkbox"/> Topiramate
<input type="checkbox"/> Ethosuximide	<input type="checkbox"/> Phenobarbital	<input type="checkbox"/> Valproic acid
<input type="checkbox"/> Gabapentin	<input type="checkbox"/> Phenytoin	<input type="checkbox"/> Vigabatrin
<input type="checkbox"/> Lacosamide	<input type="checkbox"/> Pregabalin	<input type="checkbox"/> Zonisamide
<input type="checkbox"/> Other, i.e. _____		
  
- Has it ever occurred to you that you could not prescribe your preferred AED?
  - No
  - Yes, because:
    - Unavailability
    - No coverage by insurance
    - Patient objection
    - Other, i.e. \_\_\_\_\_

- Do you ever prescribe AEDs to brain tumor patients without epilepsy, solely as prophylaxis? Choose one option
  - No
  - Yes, sometimes as perioperative prophylaxis
  - Yes, always as perioperative prophylaxis
  - Yes, sometimes during the end-of-life phase
  - Yes, always during the end-of-life phase
  - Yes, sometimes, this could be any moment during the course of the disease
  - Yes, always during the course of the disease

**Part 4) Organisation of care**

- Who treats patients with brain tumors and epilepsy in your institute? Multiple options possible
  - Neuro-oncologist
  - General neurologist
  - Epileptologist
  - Neurosurgeon
  - Radiation Oncologist
  - Medical Oncologist
  - Other, i.e.: \_\_\_\_\_
- Is there a specific care pathway in your institute for patients with brain tumors having epilepsy?
  - No
  - Yes, namely: \_\_\_\_\_
- What is the policy in your institute regarding patients with a brain tumor and *pharmacoresistant* epilepsy? Multiple options possible
  - I treat these patients myself
  - I refer these patients to an expert (e.g. epileptologist) within our institute
  - I refer these patients to an expert (e.g. epileptologist) outside our institute
  - Other, i.e.: \_\_\_\_\_
- Which diagnostic tool do you use most frequently to diagnose epilepsy? Choose one option
  - Patient's history and/or witness accounts
  - EEG
  - Event recording (video)
- Do you routinely use EEG to diagnose brain tumor-related epilepsy?
  - No
  - Yes
- Which tools do you commonly use in daily clinical practice for monitoring a patient with brain tumor-related epilepsy?
  - Clinical history (by the physician or nurse) only
  - Clinical history (by the physician or nurse) plus seizure diary
  - Clinical history plus seizure diary plus neurocognitive testing
  - Other (please specify)
- Do you monitor AED drug levels in follow-up of patients with brain tumor-related epilepsy? Choose one option
  - No
  - Rarely
  - Sometimes
  - Often
  - Always

**Part 5) AED withdrawal**

- Do you ever consider reducing the number of AEDs in patients with brain tumor-related epilepsy who are seizure free after antitumor treatment?
  - No
  - Yes
  
- Do you ever consider reducing the AED dose in patients with brain tumor-related epilepsy who are seizure free after antitumor treatment?
  - No
  - Yes
  
- Do you routinely consider complete AED withdrawal in patients with BTRE who are seizure free after anti-tumor treatment?
  - No
  - Yes, in the following patients:
    - Meningioma
    - Low-grade glioma
    - High-grade glioma
    - Solitary brain metastasis
    - Multiple brain metastases
  - Other, i.e. \_\_\_\_\_
  
- Which factors are crucial to you when determining whether or not patients are suitable for AED withdrawal?
 

Multiple options possible

<input type="checkbox"/> Period of seizure freedom	<input type="checkbox"/> Presumed risk of seizure relapse
<input type="checkbox"/> Tumor type	<input type="checkbox"/> AED side effects
<input type="checkbox"/> Seizure severity	<input type="checkbox"/> Long-term toxicity of AEDs
<input type="checkbox"/> Time since last antitumor treatment	<input type="checkbox"/> Distress of taking daily medication
<input type="checkbox"/> Completeness of tumor resection	<input type="checkbox"/> Driving restrictions
<input type="checkbox"/> Patient preference	
<input type="checkbox"/> Other, i.e.:	

