The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma

Koekkoek, J.A.F.; Dirven, L.; Taphoorn, M.J.B.

Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma

Johan A.F. Koekkoek, Linda Dirven & Martin J.B. Taphoorn

To cite this article: Johan A.F. Koekkoek, Linda Dirven & Martin J.B. Taphoorn (2017) The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma, Expert Review of Neurotherapeutics, 17:2, 193-202, DOI: 10.1080/14737175.2016.1219250

To link to this article: https://doi.org/10.1080/14737175.2016.1219250

Accepted author version posted online: 02 Aug 2016.
Published online: 09 Aug 2016.

EXPERT REVIEW OF NEUROTHERAPEUTICS, 2017
VOL. 17, NO. 2, 193–202
http://dx.doi.org/10.1080/14737175.2016.1219250

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS

The withdrawal of antiepileptic drugs in patients with low-grade and anaplastic glioma

Johan A.F. Koekkoek[a,b], Linda Dirven[a] and Martin J.B. Taphoorn[a,b]

[a]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Neurology, Medical Center Haaglanden, The Hague, The Netherlands

ABSTRACT

Introduction: The withdrawal of antiepileptic drugs (AEDs) in World Health Organization (WHO) grade II-III glioma patients with epilepsy is controversial, as the presence of a symptomatic lesion is often related to an increased risk of seizure relapse. However, some glioma patients may achieve long-term seizure freedom after antitumor treatment, raising questions about the necessity to continue AEDs, particularly when patients experience serious drug side effects.

Areas covered: In this review, we show the evidence in the literature from 1990–2016 for AED withdrawal in glioma patients. We put this issue into the context of risk factors for developing seizures in glioma, adverse effects of AEDs, seizure outcome after antitumor treatment, and outcome after AED withdrawal in patients with non-brain tumor related epilepsy.

Expert commentary: There is currently scarce evidence of the feasibility of AED withdrawal in glioma patients. AED withdrawal could be considered in patients with grade II-III glioma with a favorable prognosis, who have achieved stable disease and long-term seizure freedom. The potential benefits of AED withdrawal need to be carefully weighed against the presumed risk of seizure recurrence in a shared decision-making process by both the clinical physician and the patient.

ARTICLE HISTORY
Received 3 May 2016
Accepted 28 July 2016
Published online
10 August 2016

KEYWORDS
Glioma; primary malignant brain tumor; epilepsy; seizures; antiepileptic drugs; drug withdrawal; surgery; radiotherapy; chemotherapy

1. Introduction

Seizures are common in patients with low-grade and anaplastic glioma, with incidence rates from 40% to 90% [1,2]. When uncontrolled, seizures may lead to morbidity as well as a negative impact on patient's health-related quality of life (HRQOL) [3]. Antiepileptic drugs (AEDs) provide the basis for epilepsy treatment. Despite the use of AEDs, 15–50% of glioma patients still experience seizures [4,5]. In patients who achieve seizure freedom, chronic use of AEDs may lead to an additional decrease in neurocognitive functioning, apart from the effect of the tumor itself and toxicities due to antitumor treatment [3]. Moreover, drug–drug interactions and other adverse effects of AEDs make long-term treatment with these agents potentially risky with numerous morbidities [6].

Antitumor treatment for glioma, which generally consists of a combination of surgery, radiotherapy, and/or chemotherapy, also contributes to seizure freedom. This has particularly been observed in patients with low-grade glioma (LGG), where tumor resection is frequently followed by prolonged seizure freedom, even in patients whose seizures were pharmacoresistant before surgery [7]. Similar results, or at least a reduction in seizure frequency, have been described after radiotherapy, temozolomide (TMZ) chemotherapy, and procarbazine, lomustine, and vincristine (PCV) chemotherapy [8]. Optimal antitumor treatment of LGGs and anaplastic gliomas with a favorable genetic profile, including the presence of a mutation of isocitrate dehydrogenase 1 (IDH-1) and a codeletion of chromosomes 1p and 19q, may result in long-term survival up to 5–15 years [9]. It is in these types of long-term-surviving glioma patients with prolonged seizure freedom where the question emerges whether AEDs should be continued endlessly. In patients with non-brain tumor-related epilepsy, the procedure of AED withdrawal is controversial, because of the fear of provoking seizure recurrence [10]. Patients with a documented seizure etiology, including a brain tumor, are thought to have an additional risk of relapse in case of AED withdrawal [11]. Although in most glioma patients, the risk of seizure recurrence may not outweigh the benefits of AED withdrawal, some studies among brain tumor patients support the notion that seizure freedom can indeed be maintained without AEDs [12].

In this review, we will discuss the potential benefits and risks of AED withdrawal in patients with LGG and anaplastic glioma. We will put this issue in the broader context of risk factors associated with the development of seizures in glioma patients, seizure outcome after antitumor treatment, the efficacy of AED treatment and their adverse effects, as well as seizure outcome after AED withdrawal in medically and surgically treated patients with non-brain tumor-related epilepsy. Finally, we will give recommendations on AED withdrawal in glioma patients for clinical practice.

1.1. Seizure risk factors

In gliomas, seizure prevalence is inversely correlated with the growth rate of the tumor [1,4]. There is also evidence that the

CONTACT Johan A.F. Koekkoek j.a.f.koekkoek@lumc.nl Department of Neurology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

epileptogenesis varies among different tumor types. In LGGs, gradual changes of the peritumoral cortex rather than direct tissue damage may underlie the development of seizures [4,13,14]. Glioneural tumors such as gangliogliomas and dysembryoblastic neuroepithelial tumors as well as supratentorial pilocytic astrocytomas and pleiomorphic xantroastrocytomas are the most epileptogenic with prevalences around 90% [15,16]. In diffuse LGGs, seizure prevalence varies between 60% and 90%. Patients with oligodendrogliomas and oligoastrocytomas, which are more often located near the cerebral cortex, are at a slightly higher risk of developing seizures compared to patients with astrocytomas [2,7]. The presence of an IDH-1 mutation in LGGs is strongly correlated with seizures as the presenting symptom, frontal lobe tumor location, and prolonged survival [17]. In general, when seizures are the only initial symptom in LGGs, they count as a favorable prognostic factor [4,18], whereas the presence of other neurological symptoms is related to a less favorable outcome [19].

Although no specific data exist regarding seizure prevalence in patients with anaplastic glioma, patients with high-grade gliomas (HGGs) present with seizures in approximately 40–60% of cases, with 20% of patients developing epilepsy during the course of the disease [20,21].

The risk for epilepsy in glioma is related to the location of the tumor as well. Due to a lower local seizure threshold, frontal lobe tumors, particularly those located in the premotor area, and temporal lobe tumors are more frequently associated with seizures compared to occipital lobe tumors. Gliomas located in the insula or other functional structures are more epileptogenic than gliomas involving midline structures [22]. LGGs, particularly those that are located near the insular cortex or supplementary motor areas, are often associated with refractory epilepsy [4,23]. Other predisposing factors for uncontrolled seizures before the start of antitumor treatment are simple partial seizures, a longer duration from seizure onset, and temporal lobe location [7,24]. On the contrary, higher age and larger tumor size are associated with a lower seizure frequency [16,25].

1.2. Seizures after antitumor treatment

1.2.1. Surgery

Tumor resection has shown to substantially improve seizure control in glioma patients. In LGGs, seizure freedom has been observed in 53–87% of the patients after surgery [5,7,26]. In a retrospective study involving 154 patients with mainly diffuse LGGs and glioneural tumors, 82% of patients were seizure free 12 months postoperative [26]. In another study that included only diffuse LGGs, 50% of the patients who had uncontrolled seizures preoperatively became seizure free after tumor resection [7]. In highly epileptogenic glioneural tumors, postoperative seizure freedom rates up to 94% were reported [27–29]. In a retrospective study involving patients with HGG, 77% of patients with preoperative seizures reported seizure freedom 12 months after tumor resection [25].

Radical tumor resection and a short duration of preoperative seizures are important predictors of postoperative seizure control in both patients with glioneural tumors and LGGs, which supports a policy aimed at an early maximally safe surgical resection [22]. In glioneural tumors, incomplete removal of the tumor and its epileptogenic zone are an important cause of uncontrolled seizures. However, in LGGs, a near-total resection is not always feasible, as these tumors are frequently located close to eloquent areas [30]. Poor seizure control postoperatively is also more common in LGG patients with simple partial seizures. However, less favorable seizure outcome has also been described in patients with glioneural tumors who showed secondary generalized seizures. In the same study, temporal tumor location and the use of intraoperative electrocorticography were not related to seizure outcome [29].

1.2.2. Radiotherapy

Radiotherapy has unequivocally shown to contribute to seizure control in a substantial part of glioma patients, although evidence is mainly based on small retrospective series that examined patients who had received focal fractionated irradiation, stereotactic radiotherapy, or brachytherapy. In addition, in some studies, a crossover with other antitumor treatments such as a surgical resection could not be excluded [8]. One larger series that included both LGGs and anaplastic gliomas treated with focal radiotherapy showed a ≥50% seizure reduction in seizure frequency in 72% of patients 3 months after treatment and in 77% at 12 months. Seizure freedom at 12 months was reached in 32% of all patients. Late-versus-early radiotherapy appeared to be predictive for a seizure reduction 3 months postradiation [31]. A randomized European Organisation for Research and Treatment of Cancer phase III trial that compared early-versus-late radiotherapy in patients with diffuse LGG or incompletely resected pilocytic astrocytoma showed that 59% of patients were seizure free 12 months after treatment in the late-radiotherapy group, compared to 75% of patients in the early-radiotherapy group [32]. Other small series in LGG patients showed seizure freedom rates ranging between 20% and 80%, although patients were evaluated at different time points [8]. Of note, significant reductions in seizure frequency have been described even during or a few weeks after radiation therapy [33].

1.2.3. Chemotherapy

Both after TMZ and PCV chemotherapy, significant reductions in seizure frequency have been observed in patients with diffuse LGG, including astrocytoma, oligoastrocytoma, and/or oligodendroglioma. In one study, seizure frequency was prospectively assessed every third TMZ cycle, showing a ≥50% seizure reduction in 48% of patients [34]. In another prospective study among 30 patients with progressive LGG, 62% of the patients with refractory epilepsy showed a seizure reduction shortly after the start of TMZ treatment [35]. Other cases suggest that TMZ may even be effective in glioma patients with intractable epilepsy, in whom anticonvulsant treatment with AEDs have failed [36]. In a retrospective study of 50 LGG patients with uncontrolled seizures, seizure reduction was reported in 44% of patients 6 months after TMZ treatment. Interestingly, seizure reduction appeared to be an independent prognostic factor for progression-free as well as overall survival. In addition, in some patients, a seizure reduction took place at an earlier stage than the radiological response,

suggesting that seizure reduction might serve as surrogate marker of tumor response [37]. In another study of 149 LGG patients, a seizure reduction was observed in 58% of patients. In one study, LGG patients receiving TMZ were compared with patients under observation. Here, 59% of the patients on TMZ had a seizure reduction, compared to 13% of the control group [38]. Small series suggest that other chemotherapeutic agents, including PCV, may also contribute to a seizure reduction [39,40].

1.3. Efficacy of AED treatment

The choice of a specific AED in glioma patients depends on several factors, including seizure type, age, sex, comorbidity, side effects, and possible interactions with antitumor treatments and other drugs. Seizures that arise from a brain tumor are in fact all symptomatic seizures that are focal in onset, even when they present as a generalized seizure. In the general population of adult patients with focal seizures, the highest evidence is available for levetiracetam, phenytoin, carbamazepine, and zonisamide [17,41]. However, for patients with glioma, high-quality data on specific AED treatments are lacking. Levetiracetam is nowadays a first-choice agent in glioma patients due to its rapid titration, good tolerability, and lack of interactions with other drugs [30,42]. Seizure freedom has been reported in 65–91% of glioma patients on monotherapy with levetiracetam, although follow-up times ranged between 1 and 13 months. In a randomized phase II trial comparing levetiracetam with pregabalin, AED monotherapy treatment failed in approximately one-third of the participants in both groups, mostly due to drug side effects. Nevertheless, both drugs were considered effective as monotherapy with seizure freedom at the end of follow-up in 65% of the patients on levetiracetam and in 75% of the patients on pregabalin [43]. In addition, levetiracetam functions as an inhibitor of *O*[6]-methylguanine-DNA methyltransferase, which might positively impact survival [44]. However, these findings are not supported by recent clinical data, showing no impact of levetiracetam on survival in glioblastoma (GBM) patients [45]. Valproic acid has been examined in two studies including glioma patients, showing seizure freedom between 30% and 78%. In a retrospective study in brain tumor patients of which 77% was diagnosed with a glioma, polytherapy with valproic acid and levetiracetam led to seizure freedom in 82% of all patients [21]. Valproic acid has also been associated with an increased survival in GBM patients receiving chemotherapy with TMZ due to its supposed chemotherapy-sensitizing properties, including the inhibition of histone deacetylase. However, in a *post-hoc* meta-analysis of four large GBM trials, an improved outcome after valproic acid could not be demonstrated [20,45]. In a retrospective study involving patients with WHO grade II–III glioma treated with TMZ, valproic acid was associated with a worse progression-free survival [46]. A few small series demonstrated the efficacy of monotherapy with topiramate (67% seizure freedom) and oxcarbazepine (seizure freedom 40–63%) [47,48]. Lacosamide may be effective as add-on therapy, with seizure freedom described in 44% of glioma patients [49]. Currently, there is a general consensus that in glioma patients, non-cytochrome P450 enzyme-inducing AEDs such as levetiracetam and valproic acid are preferred over older enzyme-inducing AEDs, such as phenytoin, carbamazepine, and phenobarbital, as the older AEDs may show unwanted interactions with other drugs including chemotherapeutic agents.

1.4. Adverse effects of AED treatments

AED side effects are reported in 20–40% of glioma patients, which is considerably more than in patients with non-brain tumor-related epilepsy [50]. The high prevalence of side effects may be caused by interactions with other drugs, such as corticosteroids, chemotherapeutic agents, and radiation therapy, and are mostly described in patients on enzyme-inducing AEDs [50]. For example, cutaneous drug reactions including mild drug rashes, but also Stevens–Johnson syndrome and toxic epidermal necrolysis, are seen most frequently in patients treated with phenytoin, carbamazepine, or lamotrigine in combination with valproic acid [42]. Drowsiness is very common in patients treated with phenobarbital, phenytoin, or carbamazepine [51].

Although nonenzyme-inducing AEDs have less interactions with other drugs, they may cause serious side effects as well. Somnolence, dizziness, and infection are commonly seen in patients on levetiracetam, although the etiology of the latter symptom remains unclear. Dizziness and cardiac conduction defects are described in patients on lacosamide. Somnolence, dizziness, and weight loss are reported in patients on zonisamide, and topiramate is associated with somnolence and dizziness as well. Blood dyscrasias can be seen in any AED, although leukopenia is mostly seen in patients on carbamazepine. Apart from weight gain and liver-enzyme abnormalities, valproic acid may lead to thrombocytopenia as well as leukopenia, particularly when combined with TMZ or PCV chemotherapy [42,52]. Due to its enzyme-inhibiting characteristics, valproic acid may cause increased levels of other AEDs, such as phenytoin or phenobarbital.

AEDs may also cause fatigue, cognitive and mood disturbances, and behavioral changes. According to a survey among brain tumor patients, fatigue and problems with memory and concentration affect more than 50% of the patients. However, it often remains unclear whether these symptoms are attributable to the tumor itself, its treatment, the occurrence of seizures, or the use of AEDs [42]. In LGGs, long-term cognitive abnormalities are experienced in up to 90% of patients [53]. A twofold increase in suicidal behavior or thoughts is reported in patients taking AEDs [54]. In patients on levetiracetam, 1–10% reports behavioral effects such as depression, nervousness, hostility, and anxiety [55]. In one study, phenytoin and carbamazepine led to impaired attention speed and memory, compared to patients who were not on AEDs [56]. In another study, participants on carbamazepine performed poorer than those without AEDs on tests of memory, attention, and cognitive speed [57]. In a population of 154 patients with LGG and epilepsy, significant reductions in both cognitive dysfunction and HRQOL were seen compared to healthy controls. The

cognitive disturbances could be attributed to the use of AEDs, whereas the decline in HRQOL was ascribed to a lack of seizure control [3].

In summary, a variety of side effects, both mild and severe, frequently affect glioma patients on AEDs. Eventually, patients have to discontinue or change their AED treatment in a majority of cases [50]. Although nonenzyme-inducing AEDs show less drug–drug interactions compared to the older AEDs, one needs to be aware of the more subtle adverse effects on mood, behavior, and cognition. Next to the achievement of seizure control, a reduction of side effects is essential as well, in order to optimize HRQOL in glioma patients with seizures.

1.5. Risks of AED withdrawal

1.5.1. Withdrawal in patients treated with AEDs only

Ideally, patients with epilepsy become seizure free without the burden of continuously taking AEDs. In glioma patients, this issue is particularly relevant to LGG patients who may achieve sustained seizure freedom in case of successful antitumor treatment. In these patients, the question may emerge whether the potential adverse effects of AEDs outweigh the risk of seizure recurrence after AED discontinuation.

Due to the fear for renewed seizures, patients and their clinical physicians may be cautious in withdrawing AEDs. In patients with non-brain tumor-related epilepsy, the risk of seizure recurrence is indeed increased the first year after AED withdrawal, particularly in the first 3 months [58]. In a meta-analysis of 20 studies examining the effect of AED withdrawal on seizure outcome after 2-year seizure remission in medically treated patients, seizure recurrence rates ranged from 12% to 66% [58,59]. However, several studies showed that patient's long-term seizure outcome was not affected after AED withdrawal [10,60]. In a study that followed patients with childhood epilepsy who attempted AED withdrawal, less than 1% of the patients developed intractable seizures after AED withdrawal [61]. Predictors for seizure recurrence after a minimum remission of 2 years in patients with a history of epilepsy include AED polytherapy, having experienced seizures after the start of AED treatment, longer duration of active epilepsy, and having an abnormal electroencephalogram (EEG) [58,62,63]. Especially, a history of primary or secondary generalized tonic–clonic seizures is found to be a risk factor for seizure recurrence after withdrawal, although some studies report that focal seizures are an independent predictor for relapse as well [6,59,62,64]. Moreover, the risk of seizure recurrence is reported to depend on the specific AED being withdrawn, with a particularly high risk of relapse after discontinuation of phenobarbital [65].

A higher risk of seizure recurrence in patients with focal epilepsy might be related to an underlying etiology. In the larger withdrawal studies in patients with epilepsy treated with AEDs only, presence of an underlying neurological condition or abnormalities on computed tomography scan has been associated with a higher relapse risk after AED discontinuation [6,64]. According to the guidelines of the Italian League Against Epilepsy, a documented etiology of seizures is of limited relevance when deciding to discontinue AEDs, if this is the only negative prognostic factor [62]. However, we think the findings in medically treated epilepsy do not directly translate to the glioma population.

1.5.2. Withdrawal in surgically treated patients

Evidence on seizure outcome after AED withdrawal in surgically treated patients with epilepsy is mostly based on studies in patients with temporal lobe epilepsy. In a cohort of 88 patients who had undergone a temporal lobectomy for intractable epilepsy, AED discontinuation was attempted in patients with seizure freedom for at least 1 year. Nine percent of patients had an underlying lesion, but any further specification was lacking. Thirty-four percent of patients developed new seizures during or after AED withdrawal. Discontinuation of AEDs was more successful in patients with younger age and those with a shorter disease duration [66]. In another study that reviewed 171 patients undergoing resection for mesial temporal lobe epilepsy, seizures recurred in 59% after withdrawal. Patients in whom AED reduction took place after 10 months of remission after resection were at lower risk of developing seizure relapse. This effect was previously described as the 'running-down phenomenon,' suggesting that seizures that occur during the first months after surgery finally remit [67]. Interestingly, in a study including 396 patients who had undergone surgical resection for intractable seizures, one-third of patients who reduced AEDs had seizure recurrence which was comparable to those who continued AEDs [68].

In general, AED withdrawal in patients who underwent epilepsy surgery does not seem to significantly increase the risk for seizure recurrence. However, seizure outcome in most post-surgery studies needs to be interpreted with caution due to a potential selection bias in the withdrawal group toward patients with a higher likelihood of surgical success [69].

Incomplete removal of the epileptogenic source is a well-known predictor of unfavorable seizure outcome after surgery [70]. Apart from age >30 years and longer disease duration, other factors associated with a higher risk of seizure recurrence after withdrawal are persistent auras, seizure relapse before withdrawal, and postoperative EEG abnormalities [51]. So far, there are no indications that patients in whom seizures recur after withdrawal are at an increased risk of developing intractable epilepsy after surgery. Also, the risk for sudden death in epilepsy (SUDEP) after AED withdrawal is thought to be low, although there are incidental cases of SUDEP following epilepsy surgery in patients who had been documented as seizure free [71].

1.6. General advantages of AED withdrawal

There are several reasons for patients to prefer AED withdrawal in case of seizure freedom, including avoidance of long-term complications, side effects, teratogenic risk, costs, and the need for follow-up care for the epilepsy. Cognitive functioning may substantially improve after AED withdrawal. In a randomized controlled study in adult patients on monotherapy with carbamazepine or valproic acid, withdrawal of carbamazepine significantly improved 30-min recall, while

withdrawal of valproic acid significantly improved performance of immediate word span [72]. In the Akershus study that followed 160 patients who were seizure free for more than 2 years, normal performance on all neuropsychological tests increased from 11% before AED withdrawal to 28% after withdrawal [10]. No improvement in HRQOL was observed after withdrawal, which was in line with the Medical Research Council withdrawal study [60]; however, the Akershus study only included patients on AED monotherapy. In another study that included both patients on mono- and polytherapy with AEDs, HRQOL scores were higher in the withdrawal group compared to the non-withdrawal group. Although not systematically examined, improved HRQOL in this study might be explained by a reduction in adverse effects including cognitive dysfunction [73]. Compared to seizure control, adverse effects of AEDs appear to be a more important determinant of HRQOL in patients with intractable epilepsy. Moreover, patients with epilepsy report worse HRQOL compared to people with other chronic illness [73].

Additional evidence for cognitive improvement after withdrawal comes from several studies in pediatric patients. Psychomotor speed improved significantly at 24 months after AED withdrawal in seizure-free children operated for intractable epilepsy [74]. In another cohort of 301 children that underwent epilepsy surgery, AED withdrawal led to improved postoperative Intelligence Quotient scores, independent of other determinants of cognitive outcome [75].

Although not systematically examined in glioma patients, AED withdrawal in medically and surgically treated patients who achieve seizure freedom thus seems to lead to a substantial improvement in several domains of cognitive functioning.

1.7. AED withdrawal in glioma patients

Due to their infiltrative nature, all gliomas eventually tend to recur after antitumor treatment. Apart from an increased risk of seizure recurrence in patients with symptomatic or localization-related epilepsy, it is likely that there is an additional risk of seizure recurrence in patients with glioma, due to the presence of residual tumor after treatment or renewed tumor growth. Studies that have examined the association between tumor recurrence and seizure recurrence, however, show controversial results. In a study that followed 332 LGG patients after tumor resection, seizure recurrence after an initial period of seizure freedom was strongly related to tumor progression. The estimated hazard ratio for tumor progression, if seizures had recurred, compared with absence of seizure recurrence was 3.80 (95% confidence interval 1.74–8.29) [7]. However, in another study of 508 LGG patients undergoing resection, postoperative seizure relapse was not associated with tumor progression [5]. Nonetheless, given the natural course of the disease, we assume that some risk of seizure recurrence will always exist in patients with glioma, even after antitumor treatment.

Although the evidence is scarce, a few studies evaluated the effect of postoperative AED withdrawal in glioma patients (Table 1). In a retrospective chart review of 169 patients with brain tumors (mostly glioma) or meningioma, AEDs were withdrawn in 34% of patients. Seizure recurrence was seen in 12.5% of a group of patients who either withdraw AEDs or never had started AEDs. Interestingly, patients who did not withdraw AEDs showed seizure relapse in 48% of cases. In other words, seizure recurrence was strongly related to the continuation of AEDs. As AED continuation frequently occurred in patients with temporal located tumors or who had undergone an incomplete resection, this effect most likely reflected the physician's decision to continue AEDs in patients at high risk of seizure recurrence. Furthermore, the study included patients with a history of epilepsy as well as patients without epilepsy who received prophylactic AED treatment perioperatively [12]. In a second study of postoperative AED withdrawal among 62 children with various types of brain tumors, including 37 LGGs, seizures recurred in 17 patients (27%) within a median time of 8 months after withdrawal. All children had a preoperative history of at least one seizure. In case of seizure recurrence, renewed seizure control could not be reached in only 2 of 17 patients due to poor medication compliance [76]. A third study examining seizure outcome after tumor resection showed seizure freedom in 82% of patients after 1 year (Engel Class I). Among all 207 patients, 154 had a neuroepithelial tumor and 53 had a glioma. In 40% of patients, AEDs could be discontinued, although seizure recurrence rate in the withdrawal group was not reported.

Table 1. Current evidence for AED withdrawal in brain tumor patients.

Study	Design	Population characteristics	Withdrawal policy	Seizure outcome
Das et al., 2012	Retrospective	169 adult patients with brain tumors (meningioma 112; LGG 57), of which 57 had epilepsy; underwent resection between 2004 and 2005	AED withdrawal or AEDs never started in 111 (meningioma 87, LGG 24) of which 16 had history of epilepsy	Seizure occurrence in 11/111 patients (9%)
			AED continuation in 58 (meningioma 25, LGG 33) of which 41 had history of epilepsy	Seizure occurrence in 28/58 patients (48%)
Khan et al., 2006	Retrospective	62 children with brain tumors (LGG 37) and history of ≥1 seizure, operated between 1985 and 2004	Withdrawal over period of 6-8 w after a median seizure-free period of 1.3 y (range 0.1–11 y)	Seizure recurrence in 17/62 patients (27%) within median time of 0.8 y (range 0.06–7.7 y)
Luyken et al., 2003	Retrospective	207 children and adult patients with low-grade brain tumors (WHO grade I–III glioma 51; other [mostly neuroepithelial] 118) and intractable epilepsy, underwent resection between 1988 and 1999	Withdrawal in 67/169 (40%) patients who had become seizure free	Seizure recurrence in 18/169 (11%) patients who had become seizure free (unknown seizure recurrence rate in withdrawal group)

w: week; y: year; LGG: low-grade glioma.

Of all patients who became seizure free, only 11% had seizure recurrence, mostly after 3–4 years [26]. All three studies did not provide any data on the frequency of serious adverse effects, such as status epilepticus or death, after AED withdrawal.

So far, there have been no prospective studies on the withdrawal of AEDs in glioma patients. One observational study is ongoing in the Netherlands, exploring the decision-making process on continuation or withdrawal of AEDs in patients with LGG and anaplastic glioma. In patients who have undergone antitumor treatment, including resection, radiotherapy, or chemotherapy, the clinical physician will discuss the option of AED withdrawal with the patient in case they have shown stable disease and seizure freedom for at least 1 year. Given the lack of evidence on the feasibility and safety of AED withdrawal in these patients, the investigators purposefully chose a non-randomized design [77]. This study should eventually give more insight in patient's willingness to withdraw AEDs, the safety of AED withdrawal in glioma patients as well as the risk of seizure recurrence in relation to renewed tumor growth.

2. Recommendations for AED withdrawal in glioma patients

2.1. General recommendations

In general, it is recommended to avoid AED withdrawal in patients with a high risk of seizure recurrence. However, predicting the precise risk of seizure recurrence remains very difficult in patients with glioma. As we have shown, seizure relapse risk depends on multiple factors including, but not limited to, tumor grade, location, seizure type, type of antitumor treatment, and the extent of a surgical resection. Unlike patients with non-brain tumor-related epilepsy, in glioma patients, seizure risk strongly varies during the course of the disease, being highly influenced by the patient's tumor status and its treatment.

The question whether the seizure relapse risk is acceptable or not, largely depends on the patient's preferences. For example, some patients explicitly ask the clinical physician to withdraw AEDs after a seizure-free period, due to side effects, the inconvenience of taking medication, or for financial reasons. Others will prefer AED continuation even in the absence of seizures due to fear of new seizures after withdrawal, seizure-related injuries, or suspension of their driver's license [63,78]. Furthermore, the psychosocial impact of discontinuing AEDs should not be underestimated. The fear of seizure recurrence will continue to exist in many patients, as lifelong seizure freedom will never be guaranteed. This holds particularly true for glioma patients, in whom seizure recurrence might induce additional fear of renewed tumor growth. In case seizures indeed recur, this may have a profoundly negative psychosocial impact and, as a consequence, reduce patient's HRQOL [58]. Patients may also fear the development of intractable epilepsy or SUDEP, although there are no indications that AED withdrawal itself negatively affects long-term seizure outcome or increases the occurrence of seizure-related fatalities [69,79]. We outlined the most essential factors that should be considered before withdrawing AEDs in patients with glioma (Table 2).

2.2. Timing of AED withdrawal

Another important issue is the timing of AED withdrawal. Until today, there is no evidence on when to initiate withdrawal in glioma patients. In patients with non-brain tumor-related epilepsy who underwent epilepsy surgery, policies toward AED withdrawal appear to differ substantially in clinical practice. In a Canadian survey, 24% of epileptologists waited more than 2 years before complete AED withdrawal was initiated. Patient's request to withdraw, presence of mesial temporal sclerosis, and a normal EEG were factors favoring withdrawal, whereas abnormal EEG findings, persistent auras, postoperative seizures, and desire to resume driving were important factors against AED withdrawal [80]. Likewise, in a US survey, 62% of respondents would start withdrawal after more 2 years of seizure freedom [81]. A more recent survey showed that 54% of physicians already started tapering within a 6-month period of seizure freedom, which was more rapidly compared to other surveys [82]. In general, policies toward AED withdrawal after successful epilepsy surgery have been more proactive during the last two decades [83]. According to a recent Cochrane review, there is no evidence regarding the optimal timing of AED withdrawal in patients who have achieved seizure freedom, although most studies suggest to start withdrawal not before a seizure-free period of 1–2 years [62,63,84]. One study showed there is no additional benefit from delayed AED withdrawal after a minimum seizure-free period of 3 years [63].

For glioma patients, a minimum period of 1-year seizure freedom after the end of antitumor treatment seems to be appropriate. Given the potentially higher risk of seizures in patients with renewed tumor growth, clinically and radiologically stable disease is an important prerequisite for AED withdrawal as well. Similar conditions are applied in the ongoing AED withdrawal study in patients with LGG and anaplastic glioma. In case patients show seizures after antitumor treatment, a seizure-free period of at least 2 years is required [77]. In clinical practice, typically patients with LGG or anaplastic glioma with a favorable prognostic profile will meet these criteria.

Currently, there is also insufficient evidence in adult patients on the duration of the tapering period, both for glioma patients and the general epilepsy population [85]. An ongoing prospective study randomizing epilepsy patients on AED monotherapy to a slow (160 days) or rapid (60 days) withdrawal schedule aims to better define the optimal length of the withdrawal period [86].

3. Expert commentary

Withdrawing AEDs in glioma patients with epilepsy is a controversial issue, as the presence of a symptomatic lesion is generally associated with an increased risk of seizure recurrence. The infiltrative aspect of the tumor and its natural

Table 2. Factors to consider before withdrawing antiepileptic drugs in glioma patients.

		Lower risk of seizure recurrence/ higher benefit from AED withdrawal	Higher risk of seizure recurrence/lower benefit from AED withdrawal
Tumor-related factors	Tumor grade and molecular-genetic profile	Anaplastic glioma and GBM	Low-grade glioma and glioneural tumors
	Tumor location	Midline, occipital lobe	Insular, frontal, and temporal lobe
	Duration of stable tumor disease after antitumor treatment	Long-term stable disease	Short-term stable disease
	Patient's prognosis at time of withdrawal	Low risk of short-term tumor recurrence	High risk of short-term tumor recurrence
Seizure characteristics	Seizure type	Generalized seizures	Partial seizures
	Seizure frequency before development of seizure freedom	Low seizure frequency	High seizure frequency
	Initial seizure severity	No history of status epilepticus	History of status epilepticus
	Duration of seizure freedom	Long-term seizure freedom	Short-term seizure freedom
Antitumor treatment	Type of antitumor treatment	Resection	Radiotherapy or chemotherapy
	In case of surgical resection: extent of resection	Total resection	Subtotal or partial resection
Side effects	Short-term and long-term AED side effects	Serious side effects affecting daily life	No/limited side effects
	Drug–drug interactions	Unwanted drug–drug interactions with for example dexamethasone or chemotherapy, particularly enzyme-inducing AEDs	No/limited interactions or use of valproic acid or levetiracetam during TMZ treatment in GBM, as it might affect survival
	Teratogenic risk	AEDs (especially AED polytherapy or use of valproic acid or carbamazepine) in women of childbearing age	Women of non-childbearing age/men
Patient-related factors	Possible psychosocial impact of epilepsy and using AEDs	Experiencing inconvenience of taking AEDs; feeling medicalized due to long-term use of AEDs	Risk of being stigmatized in case of a seizure; fear of seizure-related injuries
	Effect of withdrawal or seizure relapse on driver's license	No suspension of driver's license during or after AED withdrawal	Fear of losing driver's license in case of seizure relapse
	Financial burden of long-term AED use	Limited insurance coverage leading to substantial expenses	AEDs fully covered by medical insurance

AED: Antiepileptic drug; TMZ: temozolomide.

tendency to recur poses an additional risk for seizures. However, patients may achieve complete seizure freedom after having received antitumor treatment, particularly after a macroscopically complete resection. AED side effects as well as drug–drug interactions may negatively influence patient's HRQOL. Furthermore, studies in patients with non-brain tumor-related epilepsy show that cognitive functioning may significantly improve after AED withdrawal. The decision to withdraw or continue AED treatment is eventually up to the patient and the clinical physician. The potential benefits of AED withdrawal should be individually weighed against the presumed risk of seizure recurrence. In clinical practice, AED withdrawal is mainly recommended for patients with LGG including neuroepithelial tumors, or patients with anaplastic glioma with a favorable prognostic profile and expected multi-year survival.

4. Five-year view

Most evidence for seizure outcome after AED withdrawal is nowadays derived from patients with medically or surgically treated epilepsy. However, there is a strong need for high-quality studies on AED withdrawal specifically applying to glioma patients. In the coming years, more data are expected on the feasibility of AED withdrawal in the glioma population. Currently, there is one ongoing study examining the decision to withdraw or continue AEDs in a selected group of LGG and anaplastic glioma patients who have achieved long-term seizure freedom. Hopefully, this study will also shed some light on the association between seizure recurrence and tumor progression. To further understand why, when, and how seizures do develop during the course of the disease, careful monitoring of seizures is essential. Therefore, future glioma trials should standardly include uniform seizure outcome measures that not only take into account seizure frequency and seizure severity, but also patient's HRQOL. These measures may also help to define specific eligibility criteria for AED withdrawal in glioma patients.

Key issues

- Seizures are a common symptom in patients with glioma, leading to morbidity and negatively influencing patient's health-related quality of life (HRQOL).
- Antiepileptic drug (AED) side effects, including cognitive and mood disturbances, are seen in 20–40% of glioma patients.
- Tumor resection may lead to seizure freedom, particularly in patients who undergo a complete resection.
- Antitumor treatment with radiotherapy and chemotherapy may lead to improved seizure control.

- Evidence from patients with medically or surgically treated, non-brain tumor related epilepsy shows that AEDs can be safely withdrawn in a selected group of patients.
- The withdrawal of antiepileptic drugs (AEDs) is a controversial issue in glioma patients with epilepsy, as the presence of a symptomatic lesion is generally related to an increased risk of seizure recurrence.
- There is currently little evidence on the feasibility of AED withdrawal in glioma patients, based on a few retrospective studies.
- We recommend to consider AED withdrawal in patients with low-grade and anaplastic glioma with a favorable prognosis, who have achieved stable disease and long-term seizure freedom.
- Preferably, a shared decision on AED withdrawal is made by the patient and the clinical physician, where the potential benefits of withdrawal are weighed against the presumed risk of seizure recurrence.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6(5):421–430.
2. Ruda R, Bello L, Duffau H, et al. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. NeuroOncol. 2012;14(Suppl 4):iv55–iv64.
3. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. Ann Neurol. 2003;54(4):514–520.
4. Smits A, Duffau H. Seizures and the natural history of World Health Organization grade II gliomas: a review. Neurosurgery. 2011;68(5):1326–1333.
5. You G, Sha ZY, Yan W, et al. Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. NeuroOncol. 2012;14(2):230–241.
6. Afshari D, Moradian N. Evaluating the rate of recurrence of epilepsy after therapy discontinuation in 2-year seizure-free epileptic patients. Int J Neurosci. 2012;122(10):598–601.
7. Chang EF, Potts MB, Keles GE, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg. 2008;108(2):227–235.
   • **Retrospective study on the effect of surgical resection on seizure outcome in LGG patients with epilepsy.**
8. Koekkoek JA, Kerkhof M, Dirven L, et al. Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: a systematic review. Neuro Oncol. 2015;17(7):924–934.
   • **Systematic review reporting seizure outcome after radiotherapy and chemotherapy in glioma patients.**
9. van den Bent MJ. Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma. Neuro Oncol. 2014;16(12):1570–1574.
10. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia. 2008;49(3):455–463.
11. Ramos-Lizana J, Aguirre-Rodriguez J, Aguilera-Lopez P, et al. Recurrence risk after withdrawal of antiepileptic drugs in children with epilepsy: a prospective study. Eur J Paediatr Neurol. 2010;14(2):116–124.
12. Das RR, Artsy E, Hurwitz S, et al. Outcomes after discontinuation of antiepileptic drugs after surgery in patients with low grade brain tumors and meningiomas. J Neurooncol. 2012;107(3):565–570.
   •• **Retrospective study examining the effect of AED withdrawal in adult patients with meningioma and glioma.**
13. Riva M. Brain tumoral epilepsy: a review. Neurol Sci. 2005;26(Suppl 1):S40–S42.
14. Pallud J, Le Van Quyen M, Bielle F, et al. Cortical GABAergic excitation contributes to epileptic activities around human glioma. Sci Transl Med. 2014;6(244):244ra89.
15. Thom M, Blumcke I, Aronica E. Long-term epilepsy-associated tumors. Brain Pathol. 2012;22(3):350–379.
16. Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. Epilepsia. 2013;54(Suppl 9):12–17.
17. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in brain tumors: new insights and evidence-based management. Oncologist. 2014;19(7):751–759.
18. Leighton C, Fisher B, Bauman G, et al. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol. 1997;15(4):1294–1301.
19. van Veelen ML, Avezaat CJ, Kros JM, et al. Supratentorial low grade astrocytoma: prognostic factors, dedifferentiation, and the issue of early versus late surgery. J Neurol Neurosurg Psychiatry. 1998;64(5):581–587.
20. Kerkhof M, Dielemans JC, van Breemen MS, et al. Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. Neuro Oncol. 2013;15(7):961–967.
21. van Breemen MS, Rijsman RM, Taphoorn MJ, et al. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol. 2009;256(9):1519–1526.
22. Pallud J, Audureau E, Blonski M, et al. Epileptic seizures in diffuse low-grade gliomas in adults. Brain. 2014;137(Pt 2):449–462.
23. Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. Cancer. 2004;100(12):2622–2626.
24. Koekkoek JA, Dirven L, Heimans JJ, et al. Seizure reduction in a low-grade glioma: more than a beneficial side effect of temozolomide. J Neurol Neurosurg Psychiatry. 2014;86(4):366–373.
25. Chaichana KL, Parker SL, Olivi A, et al. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. J Neurosurg. 2009;111(2):282–292.
26. Luyken C, Blumcke I, Fimmers R, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia. 2003;44(6):822–830.
   • **Study that retrospectively analyzed seizure outcome in patients with neuroepithelial tumors and intractable epilepsy undergoing resection.**
27. Thom M, Toma A, An S, et al. One hundred and one dysembryoplastic neuroepithelial tumors: an adult epilepsy series with immunohistochemical, molecular genetic, and clinical correlations and a review of the literature. J Neuropathol Exp Neurol. 2011;70(10):859–878.
28. Southwell DG, Garcia PA, Berger MS, et al. Long-term seizure control outcomes after resection of gangliogliomas. Neurosurgery. 2012;70(6):1406–1413.
29. Englot DJ, Berger MS, Barbaro NM, et al. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. Epilepsia. 2012;53(1):51–57.

30. Maurice C, Mason WP. Seizure management in patients with gliomas. Expert Rev Neurother. 2014;14(4):367–377.
31. Ruda R, Magliola U, Bertero L, et al. Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. Neuro Oncol. 2013;15(12):1739–1749.
• **Retrospective study reporting seizure outcome after radiotherapy in patients with low-grade and anaplastic glioma.**
32. van den Bent MJ, Afra D, de WO, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet (London, England). 2005;366(9490):985–990.
33. Plathow C, Schulz-Ertner D, Thilman C, et al. Fractionated stereotactic radiotherapy in low-grade astrocytomas: long-term outcome and prognostic factors. Int J Radiat Oncol Biol Phys. 2003;57(4):996–1003.
34. Pace A, Vidiri A, Galie E, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann Oncol. 2003;14(12):1722–1726.
35. Tosoni A, Franceschi E, Ermani M, et al. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. J Neurooncol. 2008;89(2):179–185.
36. Ngo L, Nei M, Glass J. Temozolomide treatment of refractory epilepsy in a patient with an oligodendroglioma. Epilepsia. 2006;47(7):1237–1238.
37. Koekkoek JA, Dirven L, Heimans JJ, et al. Seizure reduction is a prognostic marker in low-grade glioma patients treated with temozolomide. J Neurooncol. 2016;126(2):347–354.
38. Sherman JH, Moldovan K, Yeoh HK, et al. Impact of temozolomide chemotherapy on seizure frequency in patients with low-grade gliomas. J Neurosurg. 2011;114(6):1617–1621.
39. Frenay MP, Fontaine D, Vandenbos F, et al. First-line nitrosourea-based chemotherapy in symptomatic non-resectable supratentorial pure low-grade astrocytomas. Eur J Neurol. 2005;12(9):685–690.
40. Soffietti R, Ruda R, Bradac GB, et al. PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. Neurosurgery. 1998;43(5):1066–1073.
41. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551–563.
42. Armstrong TS, Grant R, Gilbert MR, et al. Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy. Neuro Oncol. 2015;18(6):779–789.
43. Rossetti AO, Jeckelmann S, Novy J, et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro Oncol. 2014;16(4):584–588.
44. Bobustuc GC, Baker CH, Limaye A, et al. Levetiracetam enhances p53-mediated MGMT inhibition and sensitizes glioblastoma cells to temozolomide. Neuro Oncol. 2010;12(9):917–927.
45. Happold C, Gorlia T, Chinot O, et al. Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. J Clin Oncol. 2016;34(7):731–739.
46. Redjal N, Reinshagen C, Le A, et al. Valproic acid, compared to other antiepileptic drugs, is associated with improved overall and progression-free survival in glioblastoma but worse outcome in grade II/III gliomas treated with temozolomide. J Neurooncol. 2016;127(3):505–514.
47. Maschio M, Dinapoli L, Zarabla A, et al. Outcome and tolerability of topiramate in brain tumor associated epilepsy. J Neurooncol. 2008;86(1):61–70.
48. Maschio M, Dinapoli L, Sperati F, et al. Oxcarbazepine monotherapy in patients with brain tumor-related epilepsy: open-label pilot study for assessing the efficacy, tolerability and impact on quality of life. J Neurooncol. 2012;106(3):651–656.
49. Maschio M, Dinapoli L, Mingoia M, et al. Lacosamide as add-on in brain tumor-related epilepsy: preliminary report on efficacy and tolerability. J Neurol. 2011;258(11):2100–2104.
50. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54(10):1886–1893.
51. Shih JJ, Ochoa JG. A systematic review of antiepileptic drug initiation and withdrawal. Neurologist. 2009;15(3):122–131.
52. Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. Neurology. 2011;77(12):1156–1164.
53. Shields LB, Choucair AK. Management of low-grade gliomas: a review of patient-perceived quality of life and neurocognitive outcome. World Neurosurg. 2014;82(1–2):e299–309.
54. Kanner AM. Suicidality and epilepsy: a complex relationship that remains misunderstood and underestimated. Epilepsy Curr. 2009;9(3):63–66.
55. Mbizvo GK, Dixon P, Hutton JL, et al. The adverse effects profile of levetiracetam in epilepsy: a more detailed look. Int J Neurosci. 2014;124(9):627–634.
56. Meador KJ, Loring DW, Allen ME, et al. Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. Neurology. 1991;41(10):1537–1540.
57. Meador KJ, Loring DW, Ray PG, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology. 2001;56(9):1177–1182.
58. Aktekin B, Dogan EA, Oguz Y, et al. Withdrawal of antiepileptic drugs in adult patients free of seizures for 4 years: a prospective study. Epilepsy Behav. 2006;8(3):616–619.
59. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? CNS Drugs. 2004;18(4):201–212.
60. Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. Lancet (London, England). 1991;337(8751):1175–1180.
61. Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. Neurology. 2005;64(6):973–975.
62. Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: guidelines of the Italian league against epilepsy. Epilepsia. 2013;54(Suppl 7):2–12.
63. Su L, Di Q, Yu N, et al. Predictors for relapse after antiepileptic drug withdrawal in seizure-free patients with epilepsy. J Clin Neurosci. 2013;20(6):790–794.
64. Hawash KY, Rosman NP. Do partial seizures predict an increased risk of seizure recurrence after antiepilepsy drugs are withdrawn? J Child Neurol. 2003;18(5):331–337.
65. Chadwick D. Starting and stopping treatment for seizures and epilepsy. Epilepsia. 2006;47(Suppl 1):58–61.
66. Kim YD, Heo K, Park SC, et al. Antiepileptic drug withdrawal after successful surgery for intractable temporal lobe epilepsy. Epilepsia. 2005;46(2):251–257.
67. Lee SY, Lee JY, Kim DW, et al. Factors related to successful antiepileptic drug withdrawal after anterior temporal lobectomy for medial temporal lobe epilepsy. Seizure. 2008;17(1):11–18.
68. Berg AT, Vickrey BG, Langfitt JT, et al. Reduction of AEDs in postsurgical patients who attain remission. Epilepsia. 2006;47(1):64–71.
69. Braun KP, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. Curr Opin Neurol. 2014;27(2):219–226.
70. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol. 2012;11(9):784–791.
71. Mansouri A, Alhadid K, Valiante TA. Sudden unexpected death in epilepsy following resective epilepsy surgery in two patients withdrawn from anticonvulsants. J Clin Neurosci. 2015;22(9):1505–1506.
72. Hessen E, Lossius MI, Gjerstad L. Improvement in verbal memory after withdrawal of carbamazepine and valproate in patients with well-controlled epilepsy: a randomized, double-blind study. Acta Neurol Scand. 2011;123(6):385–389.

73. Zou X, Hong Z, Chen J, et al. Is antiepileptic drug withdrawal status related to quality of life in seizure-free adult patients with epilepsy? Epilepsy Behav. 2014;31:129–135.
74. van Schooneveld MM, van EN, Boshuisen K, et al. Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery. Epilepsy Res. 2013;107(1–2):200–203.
75. Boshuisen K, van Schooneveld MM, Uiterwaal CS, et al. Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. Ann Neurol. 2015;78(1):104–114.
76. Khan RB, Onar A. Seizure recurrence and risk factors after antiepilepsy drug withdrawal in children with brain tumors. Epilepsia. 2006;47(2):375–379.
•• **Retrospective study on withdrawal of AEDs after antitumor treatment in children with various types of brain tumors and epilepsy.**
77. Koekkoek JA, Kerkhof M, Dirven L, et al. Withdrawal of antiepileptic drugs in glioma patients after long-term seizure freedom: design of a prospective observational study. BMCNeurol. 2014;14:157.
•• **Study protocol on the feasibility of AED withdrawal in patients with low-grade and anaplastic glioma with long-term seizure freedom after antitumor treatment.**
78. Kilinc S, Campbell C. The experience of discontinuing antiepileptic drug treatment: an exploratory investigation. Seizure. 2008;17(6):505–513.
79. Hixson JD. Stopping antiepileptic drugs: when and why? Curr Treat Options Neurol. 2010;12(5):434–442.
80. Tellez-Zenteno JF, Ronquillo LH, Jette N, et al. Discontinuation of antiepileptic drugs after successful epilepsy surgery. a Canadian survey. Epilepsy Res. 2012;102(1–2):23–33.
81. Berg AT, Langfitt JT, Spencer SS, et al. Stopping antiepileptic drugs after epilepsy surgery: a survey of U.S. epilepsy center neurologists. Epilepsy Behav. 2007;10(2):219–222.
82. Swisher CB, Sinha SR. Survey of current practices among US epileptologists of antiepileptic drug withdrawal after epilepsy surgery. Epilepsy Behav. 2013;26(2):203–206.
83. Hemb M, Velasco TR, Parnes MS, et al. Improved outcomes in pediatric epilepsy surgery: the UCLA experience, 1986-2008. Neurology. 2010;74(22):1768–1775.
84. Kerling F, Pauli E, Lorber B, et al. Drug withdrawal after successful epilepsy surgery: how safe is it? Epilepsy & Behav. 2009;15(4):476–480.
85. Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. Cochrane Database Syst Rev. 2006;2:CD005003.
86. Gasparini S, Ferlazzo E, Giussani G, et al. Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study: a pragmatic multicentre, prospective, randomized, controlled study. Neurol Sci. 2016;37(4):579–583.