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REVIEW

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Antiepileptic medications in neurosurgical practice

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Abstract

One of the earliest medical disorders to be identified is epilepsy. Strange and diverse forms of therapy have been used throughout history. A cure has not been found despite the popularity of ointments, medications, magic, enemas, exorcism, spiritualism, surgical and physical, as well as behavioural therapies. There is a notable deficiency of current literature about the management of seizures and epilepsy in neurosurgical patients, despite the fact that neurosurgeons are enrolled in the prescription of antiepileptic drugs (AEDs) for the seizures especially in perioperative periods. Neurosurgeons scope of management of epilepsy usually involve patients with either traumatic brain injury, neoplasms, subarachnoid haemorrhages, and brain abscess and infection. Depending on when they began, post-craniotomy seizures are categorised into three categories: promptly (before 24 h), early (before 1 week), and late (after 1 week). One-third of seizures can occur within the first month after a craniotomy, usually within the first 3 days, even though the risk of seizures persists for several post-operative months. There are multiple generations of AEDs, and further research is required to settle a clear recommendation for each and every case of seizures especially for hard population like the neurosurgical patients.

Keywords Craniotomy, Epilepsy, Post-operative, Seizures

Background

One of the earliest disorders to be identified is epilepsy. Strange and diverse forms of therapy have been used throughout history. A cure has not been found despite the popularity of ointments, medications, magic, enemas, exorcism, spiritualism, surgical and physical, as well as behavioural therapies. There are some beneficial therapies within this compass, but there are also some that are misguided, ineffective, deceptive, and occasionally downright dishonest. Of course, epilepsy is a demanding taskmaster for the curious. Its variable nature, ready susceptibility to environmental influences, ease of confounding with hysterical diseases, multifactorial origins, and propensity for spontaneous remission are all considerations.

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History of antiepileptic drugs (AEDs)

AEDs can be divided historically into three generations. Between 1857 and 1958, the first generation initially entered the market, mostly supported by data from clinical observations. Potassium bromide, phenobarbital, and a number of medications, such as phenytoin, ethosuximide, trimethadione, and primidone, were all derived from the barbiturate chemical structure [1]. A decision was made in the early 1960s in the USA and the European Union that would have a significant impact on future drug development. This decision was prompted by reports in the late 1950s that maternal intake of the widely prescribed hypnotic thalidomide had caused massive malformations in thousands of babies. The Kefauver–Harris Drug Amendments to the US Food and Drug Laws were signed by President John F. Kennedy in 1962, and they required businesses to present "substantial evidence" of a drug's efficacy before marketing it [1, 2]. All pharmaceutical items must receive a marketing authorization in accordance with European Union regulations

in order to be sold there since 1965 [1]. The second generation of AEDs, which were launched between 1960 and 1975 and included carbamazepine, valproate, and benzodiazepines, was chemically distinct from barbiturates [3]. Phase 4 double-blind benchmark trials comparing four standards of treatment revealed that both phenytoin and carbamazepine and can be used more effectively for treating focal seizures than the more sedative barbiturates, phenobarbital, and primidone [4]. Phenytoin and phenobarbital are still widely used in many parts of the world due in large part to their affordability despite their well-known dose-related central nervous system side effects. Phenytoin and phenobarbital have never been shown to be less effective than carbamazepine for focal seizures [4]. However, two clinically significant drawbacks exist for carbamazepine, phenytoin, phenobarbital, and primidone (which is converted to phenobarbital). They generate hypersensitivity reactions and are strong enzyme inducers, which can have clinically significant adverse medication interactions [5, 6]. Valproate was proved to be an effective treatment for hereditary (idiopathic] generalised and focal epilepsy by a clinical observations made by French physicians [7]. A randomised phase 4 study [8] found that valproate was only marginally more effective than carbamazepine for treating complex partial seizures, and it also has three other clinically significant drawbacks: as an enzyme inhibitor, it can cause harmful drug interactions; it can lead to hepatic failure in susceptible people; and it is the most teratogenic of the currently marketed AEDs. There is no evidence that any third-generation AEDs are more effective in preventing seizures than carbamazepine or valproate at treating focal or generalised seizures, respectively [9]. In over 20% of patients with new-onset epilepsy who match the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy, third-generation AEDs do not produce prolonged seizure freedom [10]. It has disappointed many patients and doctors that the treatment of frequent seizures or epileptic syndromes has not significantly improved over the past few decades. Furthermore, there are no appreciable differences between older and newer first-line AEDs in terms of the proportion of newly treated patients who experience side effects [11, 12]. The use of novel AEDs can have life-threatening adverse effects, while these are uncommon [5]. Major pharmaceutical companies have lost interest in and investment due to the challenge (and high development costs) of demonstrating large differences in clinically relevant result between new drugs and the present antiseizure medication, or even placebo in some circumstances [13]. The fact that existing AEDs have not been demonstrated to stop the development of epilepsy and that there is no proof of any disease-modifying activity raises a lot of suspicion in the medical and pharmaceutical communities [13].

On the other hand, the introduction of new drugs has enriched the armamentarium of antiepileptic medications. The presence of about 25 different drugs in the market provided the physicians with unprecedented opportunities to custom the medications for each patient according to his seizure profile [14]. However, becoming familiar with the indications, contraindications, unique characteristics, and dose regimens of 25 different medications is a difficult endeavour, and there are worries that inadequate knowledge could lead to inappropriate prescribing and its associated detrimental effects. Every practitioner has the problem of staying current with fast advancing knowledge, and even in the internet era, quick access to information does not always guarantee easy access to reliable, objective evidence. In the era of evidence-based medicine, careful evaluation of the relative benefits to hazards ratios of available medicines, based on the findings of well-designed, randomised double-blind studies, should serve as the best guidance for drug selection. Unfortunately, the fact that placebo-controlled adjunctive therapy trials are primarily created to satisfy regulatory criteria and provide little information on the comparative benefit of a medicine hinders a truly evidence-based approach to the treatment of epilepsy [14], while the vast majority of randomised active-control monotherapy trials suffer from serious methodological flaws, such as the selection of populations with inadequate syndromic diagnosis, insufficient sample size, ineffective dosing regimens, and bias in study design that might have favoured the sponsor's product [3–5, 15–17]. Furthermore, the effectiveness of treatment in a number of epilepsy syndromes has never been examined in controlled trials [17]. Because of this, selecting a medicine cannot be entirely dependent on the findings of therapeutic trials; rather, a wider variety of data must be considered. In actuality, no single pharmaceutical on the market can be suggested as the preferred course of treatment for all patients, and sensible prescribing necessitates a rigorous evaluation of both the characteristics of each drug and those of the patient. The main goal is to choose a course of action that matches the patient's characteristics the best, increases the likelihood that the patient will become seizure-free, and does so without having disproportionately negative side effects [18–20].

There is a notable deficiency of current literature about the management of seizures and epilepsy in neurosurgical patients, despite the fact that neurosurgeons are enrolled in the prescription of AEDs for the seizures especially in perioperative periods [21]. It is important to pay particular attention to the effects of AED use in neurosurgery. AEDs may result in adverse effects that could

compromise the clinical surveillance of the patient's underlying disease. On the other hand, the underlying pathology may result in the emergence of neurological symptoms that may be mistakenly attributed as a side effect of the AED [22]. AEDs may also be problematic when taken in conjunction with chemotherapy for the treatment of brain neoplasms. Although there is debate over the effectiveness of anticonvulsant prophylaxis in patients undergoing craniotomies, it is critical to provide the best post-operative seizure care in order to both prevent unanticipated complications and enhance surgical results [23].

Depending on when they began, post-craniotomy seizures are categorised into three categories: promptly (before 24 h), early (before 1 week), and late (after 1 week). One-third of seizures can occur within the first month after a craniotomy, usually within the first 3 days, even though the risk of seizures persists for several post-operative months [24]. The likelihood of epileptic seizures after a craniotomy is rather high; however, there are certain factors that increase the possibility pf post-operative seizures. Those factors include the presence of any insult during the surgery and presence of history of epileptic activity [25].

According to research conducted on animals, there are two possible pathways by which neurosurgical insults produce seizures: one is mediated by the production of free radicals, and the other is via poor ion balance across the cell membrane as a result of ischaemia or hypoxia [23].

Neurosurgery scope

Research on pharmacological prophylaxis has been sparked by the prevalence of seizures following supratentorial surgery for nontraumatic diseases; however, number of trials that were conducted in a prospective randomised manner did not show any evidence that AEDs can affect or control post-operative epilepsy. A published study gathered data from six meta-analyses published between 1996 and 2011. They investigated the safety and potency of anticonvulsant prophylaxis of seizures in neurosurgical patients; it concluded that prophylactic antiepileptics does not improve seizure control in patients undergoing craniotomy. Hence, the seizure prophylaxis should not be applied on routine basis [24].

No doubt that preoperative seizures must be controlled with treatment with antiepileptics, but the necessity of perioperative prophylaxis is debatable even if for patients with scheduled brain tumour surgeries especially if the patient has no history of seizures. A preventive drug should only be used if there is a high likelihood of the undesirable consequence and the drug is both effective in avoiding it and has a manageable risk of toxicity. Due to a lack of potency and increased side effects in a meta-analysis, the American Academy of Neurology published practice criteria in 2000 in which they did not recommend the use of AED use on prophylactic basis in newly diagnosed brain tumour patients [24].

AED therapy following neurosurgical interventions aims to lower the probability of seizures and hence prevent adverse effects on the patients. Prophylactic AEDs have been investigated in several studies to see if they could change the course of post-neurosurgical epilepsy and if they could prevent the onset of chronic epilepsy [25, 26]. The use of AEDs continues to be standard practice even though international guidelines do not recommend their use in post-operative patients for seizure control or prevention as they did not appear to protect against late seizures. Numerous studies found no statistically significant difference in the incidence of post-operative seizures between patients who received prophylactic antiepileptic treatment and those who did not, but these same studies occasionally found a high incidence of adverse drug reactions in the treated group [27–29].

Traumatic brain injury

Traumatic brain injury (TBI) frequently results in the debilitating consequence of post-traumatic seizures (PTS). They are regarded as a serious public health issue and represent 20% of all symptomatic epilepsies [30]. Early seizure occurrence (7 days after injury) ranges from 2.1 to 16.9%, and late seizure occurrence (>7 days after injury) ranges from 1.9 to greater than 30%. Secondary brain injury can result from the neurotransmitters release in an excessive manner and also a resultant elevated intracranial pressure that may follow the trauma due to oedema and or haemorrhagic insults. The increased metabolic needs can also participate in the occurrence of the secondary brain injury [31]. PTS occurrence can increase also the secondary brain injury [32, 33]. If seizures cause falls and additional injuries, late PTS might negatively affect how well patients recover from their injuries [34, 35]. Because of their greater recurrence rate, these seizures are a significant factor in readmissions [34].

Early and late seizures are believed to be caused by different but related processes. Due to the mechanical disturbance the damaging force causes, the former are typically thought of as a self-limiting entity [36]. The establishment of an epileptic focus, which causes late PTS, is thought to be the outcome of the subsequent inflammation, excitotoxicity, ischaemia, and scarring. Antiepileptic medications can be given to suppress early seizures with the expectation of stopping epileptogenesis and preventing late PTS [37]. In animal models of TBI, attempts to stop the epileptogenic process have been

successful, but it have not been yet in the clinical settings or research trials [38].

Phenytoin prophylaxis is advised during the first week according to the last recommendations of the Brain Trauma Foundation. The story is different regarding the late PTS; the latest recommendations advised against the prophylactic therapy is not advised to avoid late PTS [39]. Four randomised controlled trials checked the results of controlling of the seizure activity after long use of an AED versus placebo, but they failed to express any potential benefits of using such medications in controlling the delayed onset seizures [40–43]. Furthermore, other six trials were investigated in a Cochrane review and came out with the same conclusion that does not support the use of AED for prevention of the late fits [44]. Temkin et al. demonstrated no effect above placebo after continuing phenytoin for 24 months [40]. A supplementary review of the phenytoin group's performance on neuropsychological tests showed a significant impairment, indicating a cognitive deficiency that might be detrimental to recovery [45]. Bhullar et al. reached the same conclusion that the minimal dose of phenytoin can affect Extended Glasgow Outcome Scale compared to those who did not receive prophylaxis. Its list of side effects also includes teratogenicity, the induction of many cytochrome P450 enzymes that may result in harmful medication interactions, and potentially lethal dermatological problems [46–48]. Phenytoin's nonlinear pharmacokinetics, which are increased after TBI, make it more challenging to utilise and necessitate multiple serum concentration tests [49].

Due to a variety of positive traits, levetiracetam is increasingly given instead of phenytoin [50]. It has not been demonstrated to result in a cognitive deficit and may even enhance neuropsychological abilities like language and remembering [51, 52]. It offers a broad therapeutic window, predictable pharmacokinetics, is safe during pregnancy, and eliminates the need for serum monitoring [53]. However, levetiracetam is expensive, and some common side effects do occur in post-traumatic patients like somnolence and depression [54]. Psychosis and suicidal thoughts were recorded in two of 126 people who experienced rare, brief, but possibly harmful psychiatric side effects [54]. Close monitoring would be mandatory if the post-traumatic patient had a history of psychiatric disease [55]. Despite these issues, it was shown to be safe and well-tolerated for usage in TBI.

The Brain Trauma Foundation guidelines did not give the privilege neither to phenytoin nor to the levetiracetam as a primary medication in the early phase post-traumatic seizures as there was not enough data to support any recommendations [39]. Levetiracetam and phenytoin have been found to be equally effective at preventing early seizures in two published meta-analyses that compare them [56, 57]. The effectiveness of these medications in treating late PTS, however, does not seem to have been compared in any studies. Further studies are needed to prove the efficacy of any AED to control late PTS and to decide which AED is more effective in accomplishing such a challenging task.

Brain tumours

More than one-third of patients suffering from brain tumours present with seizures, and another 40% of patients may experience seizures within their journey of management [58, 59]. Seizures are more common in cortical tumours; epilepsy probabilities are higher in patients with temporal (86.8%) and frontal (82.0%) tumours, although the presence of a brain tumour itself does not guarantee that one would experience seizures [60].

In terms of the paediatric population, a retrospective review of infants who had supratentorial craniotomies revealed that just 12 per cent of them experienced postoperative seizures. According to the same study, women appear to be statistically more likely to experience seizures. The absence of dural closure appears to increase the likelihood of developing epilepsy [26].

It was proved that the histopathological nature can affect the incidence of epilepsy. For instance, gangliogliomas and neurogliomas have a very high incidence of seizures reaching more than 80%, also oligodendrogliomas can present with fits in nearly 70% of patients. Low-grade diffuse gliomas produces epileptogenic activity in 60% of patients, whereas over 40% of cases with glioblastomas (GBMs) could have one or more seizure activity thorough their course of management [58].

Gliomas

Alterations within the tumour and the glioblastoma's rapid development, which can promote focal epileptogenesis and exacerbate seizures that are already occurring [61]. Tumour recurrence is common in glioblastoma, and post-resection epilepsy development has been connected to tumour progression [60].

When treating glioblastoma patients for seizures, important linked factors must be taken into account. Complete seizure relief is frequently achieved by the combination of the use of AEDs together with surgery and adjuvant therapy, for seizure control [62].

In a retrospective analysis of 184 adult patients with supratentorial glioma, the incidence of epilepsy, factors influencing the development of epilepsy in these cases, and patients' reactions to AEDs were all investigated. Epilepsy incidence was assessed before, after, and every 2 months after the initial resection. AEDs can reduce the frequency of seizures in glioma patients when given over

long periods of time. It was typical to have epilepsy, and AEDs had poor short-term efficacy [60].

The activity of both AEDs and antineoplastic drugs may be altered by the pharmacological interactions between each other with an incidence of reducing their efficacy and raising the risk of adverse effects associated with both regimens. There are no particular recommendations for AEDs to guard against post-operative seizures in glioma patients. Prescriptions are frequently chosen based on the personal preferences of the neurosurgeon or neurologist. The most popular AEDs used to prevent seizures in post-surgery glioma patients are PHT, CBZ, VPA, and LEV [62].

A meta-analysis of numerous clinical trials revealed varying findings about the efficacy of AEDs. Early post-operative seizures are at a low risk with LEV and PHT, while later epilepsy is at a moderate risk. However, there was no discernible difference observed between the AEDs that were studied [63].

Retrospective analyses of 971 patients undergoing craniotomies over a 2-year period compared the incidence of seizures in patients given preventive PHT or LEV perioperatively. PHT was often utilised, while LEV was given instead of PHT if it was contraindicated. Fits recorded within the first week following a craniotomy were taken into consideration. AEDs were used to treat a total of 235 patients: 154 patients received PHT, and 81 patients received LEV. There were no known adverse events or drug interactions for any patients. The information indicates that LEV can be an alternative for those for whom PHT is contraindicated [64].

The shift from PHT to LEV monotherapy to protect against post-operative seizures in glioma patients is a safe and practical choice, according to a randomised controlled trial, because it results in fewer side effects [65].

The efficacy and safety profiles of LEV encouraged the research projects to start testing the drug as a primary and sole agent in the prophylaxis of post-operative seizures in contrast to PHT. This was tried for cases with supratentorial tumours during the perioperative phases. Prospective randomised research was conducted. When compared to the PHT group, the LEV group had a considerably lower incidence of seizures. Moreover, LEV is linked to less adverse events and appears to be more safe with more appealing safety profile [66].

Meningiomas

13 to 60 per cent of patients with intracranial meningiomas experience seizures as a common symptom. Naturally, there is a substantially decreased risk of seizures if the tumour is infra-tentorial. Risk factors for newly arising post-operative seizures include parietal meningiomas, significant peritumoural oedema, extensive intraoperative brain retraction, and obstruction of cortical arteries or veins [67].

Up to 40% of meningioma patients experience seizures prior to surgery. Following tumour removal, the majority of patients (60–90%) are able to achieve a good control for their seizure activity. Following surgery, 10–20% of patients experience new-onset seizures. A persistent risk factor for post-operative seizures is a preoperative seizure history; however, total tumour excision with avoidance of cortical injury can be beneficial. In the absence of sufficient evidence supporting methodology and drug selection for post-operative AED therapy in patients with meningioma, the general rule for pharmacological treatment of focal epilepsy should be adhered to [62].

Prophylactic AED therapy might prevent early seizures in meningiomas, but it is uncertain how it may affect late seizures and long-term outcomes. For instance, in one case control study, 180 patients without history of preoperative seizures, no statistical differences were observed regarding the occurrence of post-operative fits between the two groups of patients whether they were given AED or not [68]. Long-term AED medication is typically not advised for individuals who only had post-operative seizures in the early stages [69].

It is common practice to administer perioperative anticonvulsant prophylaxis to neurosurgical patients, especially in the initial stages of the healing process. With the seizure risk remaining for several months, more than 60% of seizures do occur in the first month following craniotomy [70], specifically in the first 3 days [70]. Despite the lack of evidence in the literature that can favour one line of treatment over another, neurosurgeons are compelled to prescribe AEDs because they are aware of the high risk of developing post-operative seizures [71]. Numerous studies on this topic have been published, but there are no clinical practice recommendations and the choice to treat or not is still currently based on the clinicians' personal preferences.

On the one hand, five randomised controlled studies that examined the prophylactic use of some old generation of AEDs in a total of 404 patients with brain tumours were discovered by a Cochrane review in 2008. Between preventative AEDs and the placebo, there were no changes in seizure outcome [29]. Additionally, utilising AEDs to prevent early or late phase post-operative seizures following the removal of supratentorial meningiomas has not been proved to be beneficial, according to a 2011 comprehensive analysis by Komotar [69]. According to a 2015 Cochrane review that included eight randomised controlled studies, there is little proof that AED medication taken beforehand helps prevent post-craniotomy seizures [71]. The limitation of the prophylactic use of AEDs in patients with brain tumours is strengthened

by the notion that they lessen drug-related side effects because it is unclear how effective they are [25, 29, 71].

On the other hand, one meta-analysis did prove some benefits for the use of post-operative AED prophylaxis especially in the short term [72]. However, it could not justify the long-term prophylaxis. The authors proposed that the difference in the effects of AED prophylaxis on short- and long-term seizure rates can be explained by a number of different mechanisms. First, when seizure risk is sharply increased due to surgical manipulation, AED prophylaxis may be useful in lowering seizure incidence in the early post-operative period. As this acutely heightened risk subsides, the effects of AED prophylaxis might lessen. Second, long-term post-operative seizures might be linked to some sort of tumour progression or recurrence which can be illustrated in radiological studies [73, 74].

Given that AEDs are ineffective at preventing seizures associated to tumour progression [75], it is probable that tumour growth will eventually cancel out any initial difference in seizure incidence between AED prophylaxis arms and control arms. The so-called "kindling hypothesis", which holds that preventing early seizures can lessen the likelihood of later seizures by reducing the establishment of a scarred epileptogenic centre, is also not supported by the long-term analysis's findings.

Aneurysmal subarachnoid haemorrhage and arteriovenous malformations (AVMs)

Patients with cerebral aneurysms have a high rate of morbidity and mortality. Since the 1970s, aneurysmal subarachnoid haemorrhage (aSAH) results have improved, but the mortality rate is still close to one-third, and survivors frequently experience cognitive damage [76–78]. As a result, it is crucial to keep these already seriously ill patients from developing new issues, such seizures. With incidence reports reaching 26 per cent, the risk of seizures increasing after cerebral aneurysmal rupture has been well-documented [76, 79, 80]. Seizures have been linked to worse outcomes for patients compared to aSAH patients who do not have one [81, 82]. As a result, prophylactic antiepileptic medication (AED) use is widespread among aSAH patients, while its efficacy has not yet been established [80, 83]. On the use of preventive AEDs in aSAH patients, there is no level I evidence [84]. The available evidence does not clearly support the usual use of prophylactic AEDs, and some reports point to associated functional results that are poorer [85, 86]. The American Heart Association's 2012 aneurysmal subarachnoid haemorrhage recommendations advise doctors to use antiepileptic drugs in the immediate aftermath of a rupture but oppose their long-term use except in high risk of seizure recurrence (Connolly et al., 2012). History of seizures, hematoma, parenchymal infarct, and a middle cerebral artery aneurysm were found to be risk factors for seizure recurrence [87].

AVMs are congenital vascular anomalies in which the arteries and abnormally convoluted and dilated veins are directly connected. The parenchyma's aberrant vascular network, or nidus, is where the shunt takes place. The first signs usually appear in the third decade of life and include neurological impairments, parenchymal haemorrhage, seizures, or headaches. Numerous population-based studies have estimated the prevalence of AVM, which is typically pegged at 1 in 100,000 [88].

In contrast to tumours, several authors proposed that stereotactic neurosurgery, rather than AEDs, might be a preferable method of controlling AVM-related epilepsy. Stereotactic radiosurgery may help control seizures through antiepileptic effects in addition to nidus obliteration because of neuromodulation. Moreover, a gliotic capsule develops around the nidus which may control the condition by isolating the surrounding parenchyma from the [62].

A retrospective review of individuals receiving AED therapy and having AVMs was conducted by certain authors. After stereotactic surgery, the likelihood of not requiring AED treatment improved dramatically, and simple partial or secondary generalised seizure types were linked to better seizure outcomes [89].

For individuals with AVM-related epilepsy, a meta-analysis has been done to evaluate invasive AVM therapy versus conservative management using solely AEDs for seizure control. They found that there is no significant difference between both strategies to control the seizures. It is obvious that a randomised controlled trials are needed to provide a recommendation in this issue [90].

Brain abscess and empyema

Up to one-third of individuals with brain abscesses experience seizures, making infectious collections like abscesses and empyemas well known as potentially epileptogenic foci [91–93]. Therefore, it is crucial to take a great care of both antimicrobial agents and seizure control medications in addition to surgical drainage of the abscesses if accessible. The seizure threshold may be lowered by quinolones like ciprofloxacin. Like the caution in cases with glioma with adjuvant therapy, caution should be directed to possible interactions between enzyme-inducing AEDs and antibiotics. Level V evidence supports recommendations for using AEDs in cases of brain abscesses and empyemas [91, 92]. Moreover, those who have an abscess still have a 92% chance of acquiring epilepsy 5 years later [25].

Conclusions

AEDs should be efficient, well-tolerated, simple to use, and free from severe medication interactions. The "gold standard" AED may not be achievable due to the numerous and diverse pathways behind epileptogenesis. Epilepsy continues to present a significant challenge especially in patients undergoing neurosurgical interventions, despite significant advancements in recent years. New-generation AEDs have been launched over the past 30 years, and some of them appear to have a favourable tolerability profile and a low risk of medication interactions [94]. PB, PHT, CBZ, VPA, ethosuximide, and benzodiazepines are among the first-generation AEDs currently on the market for the treatment of epilepsy. Second-generation AEDs include, gabapentin, oxcarbazepine, tiagabine, lamotrigine, topiramate, pregabalin, vigabatrin LEV, and zonisamide. Also, a third-generation AEDs appeared in the market, including eslicarbazepine acetate, perampanel, and lacosamide. Nevertheless, despite the therapeutic armament of both new and old AEDs, treating seizures can occasionally be challenging, particularly after structural changes that might take place during surgery [62].

When used as preventative measures in a neurosurgical environment, old AEDs are more effective at controlling early seizures, but not to the degree for the late seizures. There are not many studies on second-generation AEDs, but they are now used more than before because of their relative control of late onset seizures with appealing safety profile. A significant barrier to treating patients with brain tumours may be the presence of significant medication interactions between AEDs and chemotherapeutic medicines. The majority of AEDs and chemotherapeutic drugs undergo substantial biotransformation via the hepatic cytochrome P450 (CYP) system [95, 96]. The clinical efficacy of anticancer medications is decreased, and their clearance is increased by enzyme-inducing AEDs such phenytoin and carbamazepine. AEDs that inhibit liver enzymes, like valproic acid, can increase the toxicity of chemotherapeutic drugs by affecting how they are metabolised.

On the other hand, valproic acid seems to have a dual action in solid CNS tumours and some neuroendocrine tumours. From one side, it can control the seizures, and from the other side, it can inhibit histone deacetylase, which controls expression of tumour suppressor genes, which is a very promising strategy [97].

The pharmacokinetics of AEDs may potentially be impacted by chemotherapeutic drugs. PHT levels in individuals with brain tumours have been shown to decrease when cisplatin is combined with carmustine, vinblastine, and methotrexate. Similarly, cisplatin treatment may lower VPA and CBZ concentrations. Same for the methotrexate therapy which also can decreases serum VPA concentrations by 25%. On the other hand, PHT levels were raised by 5-fluorouracil combined with leucovorin and high-dose tamoxifen. The safety and pharmacokinetic profiles of several novel AEDs are especially promising. These qualities are crucial for the neurosurgical population in order to prevent interactions with chemotherapy, severe cutaneous reactions during radiotherapy, or confusing side effects involving the central nervous system that confuse the symptoms of the underlying pathology [62]. In this difficult-to-treat neurosurgical group, the use of new AEDs should be promoted, especially those with no hepatic excretion, and hence has a minimal risk of toxicity, and detailed studies of their efficacy should be conducted [22]. Special attention should be directed towards the verification of the efficacy of new-generation AEDs in the control of perioperative seizure activity. In a randomised double-blind controlled trial, antiepileptic drugs like zonisamide has a neuroprotective function, it was successfully tested in animals, and research should be conducted to test the efficacy and safety of such new agents in humans [62].

In conclusion, there is currently very little research on the perioperative usage of AEDs in the neurosurgical setting. This might be as a result of the various study designs, varied patient cohorts, varying drug doses, and unclear objectives. Even though it is simply a symptomatic treatment, and both neurologists and neurosurgeons still recommend AEDs for seizure prophylaxis. The goal should be to comprehend the causes of epileptogenesis and develop therapies to inhibit it in order to effectively avoid post-operative seizures. Finally, despite the fact that patients' quality of life has significantly improved thanks to the vast therapeutic arsenal at their disposal, the goal of seizure freedom without side effects is still a long way off. Therefore, the quest for novel, more focussed, and better tolerated medications is ongoing, and future research should be guided by a greater understanding of the mechanisms producing epilepsy.

Abbreviations

AED	Antiepileptic drugs
aSAH	Aneurysmal subarachnoid haemorrhage
AVMs	Arteriovenous malformations
CBZ	Carbamazepine
LEV	Levetiracetam
PB	Phenobarbitone
PHT	Phenytoin
PTS	Post-traumatic seizures
TBI	Traumatic brain injury
VPA	Valproic acid

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