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Neuro-Oncology Practice Clinical Debate: long-term antiepileptic drug prophylaxis in patients with glioma

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Abstract

Patients with primary brain tumors often experience seizures, which can be the presenting symptom or occur for the first time at any point along the illness trajectory. In addition to causing morbidity, seizures negatively affect independence and quality of life in other ways, for example, by leading to loss of driving privileges. Long-term therapy with antiepileptic drugs (AEDs) is the standard of care in brain tumor patients with seizures, but the role of prophylactic AEDs in seizure-naive patients remains controversial. In this article, experts in the field discuss the issues of AED efficacy and toxicity, and explain their differing recommendations for routine use of prophylactic AEDs.

Keywords

antiepileptic | brain tumor | glioma | prophylaxis | seizure

A 40-year-old man with newly diagnosed left frontotemporal anaplastic oligodendroglioma, isocitrate dehydrogenase (*IDH*) mutant and 1p/19q codeleted, without any history of seizure, received prophylactic antiepileptic therapy for 1 week following craniotomy and subtotal tumor resection. He now presents to your clinic to discuss further management. Would you advise him to continue antiepileptic drug (AED) therapy long term or discontinue it unless a seizure occurs?

Position: Discontinue Antiepileptic Prophylaxis

Drs Nagpal, Hixson, and Stocksdale

In this patient with an infiltrating glioma, seizures are a valid concern. The reported frequency varies widely,[1] but patients with intracranial neoplasms are known to be at increased risk of seizures. Low-grade supratentorial CNS tumors seem to confer the highest risk, whereas more aggressive primary tumors and intracranial metastases increase risk to a lesser degree.[1] Preventing the onset of tumor-associated epilepsy in this population is desirable because it would avoid physical and psychological trauma, caregiver burden, and health care costs associated with seizures. The routine use of prophylaxis, however, requires an agent that effectively decreases the risk or severity of brain tumor-associated seizures with an acceptable toxicity profile and minimal interaction with tumor treatments. To date, the evidence available has failed to demonstrate that any AED reduces the long-term risk of new-onset seizures in patients with brain tumors[2]. Lack of demonstrated efficacy in tumor patients and the adverse effects associated with their use support our recommendation *against* the use of long-term prophylactic AEDs in this setting.

As this case demonstrates, AEDs are commonly prescribed by neurosurgeons in the perioperative period even in seizure-naive patients to reduce the risk of craniotomy-associated seizures. This practice was supported initially by a randomized, double-blind, placebo-controlled study that demonstrated a significant reduction in early postcraniotomy (days 1-30) seizures in patients treated prophylactically with phenytoin.[3] However, this study included only a small number of patients with intracranial tumors and failed to demonstrate benefit in this specific subgroup. More recently, a Cochrane review of 10 RCTs inclusive of 1815 seizure-naive patients undergoing craniotomy found no consistent evidence that prophylactic perioperative AEDs decrease the risk of seizure, other adverse events, or death.[2] Emerging data demonstrate an increased risk of intraoperative seizures in patients undergoing awake craniotomy, with incidence of up to 54% reported in some institutions.[4] However, in this multicenter study the overall risk of intraoperative seizure was identical (12%) regardless of whether patients received perioperative antiepileptics. Nonetheless, 63% of surveyed neurosurgeons reported routinely prescribing AEDs perioperatively to reduce the risk of craniotomy-associated seizures.[5] Given their widespread use at the time of resection despite unclear benefit, patients often present to neuro-oncologists having already been started on an AED. The often more daunting question of whether to *discontinue* AEDs prophylaxis then falls to the neuro-oncologist.

Nearly 20 years ago, the American Academy of Neurology (AAN) endorsed a practice parameter that discouraged prophylactic AEDs in patients with newly diagnosed brain tumors and recommended tapering or discontinuing perioperative AEDs 7 days after resection.[6] These guidelines were based on 4 RCTs and 8 cohort studies, none of which demonstrated a benefit from prophylaxis. The authors' meta-analysis of the 4 RCTs similarly showed no effect of AED prophylaxis on seizure incidence (odds ratio [OR] 1.09; 95% CI, 0.63-1.89). The earliest study included in the meta-analysis was North's 1983 report discussed previously that demonstrated a reduction in early (within 30 days) postcraniotomy seizures (although not in the tumor subgroup).[3] Seizure-free participants were continued on an AED or placebo for up to 12 months, but AED prophylaxis did not reduce the frequency of seizures from postoperative day 31 through 12 months. Further, the included studies were limited by insufficient statistical power, heterogeneous AED groups, exclusion of surgical candidates, pooling of multiple tumor types, and unclear follow-up. Two of the 4 trials were terminated at an interim analysis because of futility.

Despite the lack of evidence supporting prophylaxis, the AAN guidelines have not been widely adopted in practice. In a Canadian retrospective study conducted after the guidelines were published, 46.8% of brain tumor patients who received an AED perioperatively were continued on AED prophylaxis 3 months later.[7] The authors hypothesize this may be due to "prescribing inertia," in that it is simpler to continue a drug than it is to discuss stopping a drug another physician has started. Kouladjian et al termed this "*devolving responsibility*," when multiple health care providers expect management to be performed by another group of providers; this often leads to no health care provider taking responsibility for the management.[8] Additionally, physicians may be employing risk avoidance because a seizure will likely occur in a minority of patients and could be potentially "blamed" on the AED withdrawal, even if the evidence supports the practice of discontinuation. Indeed, a retrospective analysis showed no difference in seizure risk among patients never treated with AEDs (33.3%), tapered off perioperative AEDs (34.3%), and those continued on AEDs (37.9%), suggesting seizures after AED withdrawal should not be attributed to discontinuation of prophylaxis.[9]

Position: Continue Long-Term Seizure Prophylaxis With Antiepileptic Drugs

Drs Shivaprasad, Rai, and Tremont-Lukats

Seizure prophylaxis for brain tumor AEDs can start before or during surgery and continue for a time that physicians can define based on experience, evidence-based guidelines, or both. It is a practice that is highly variable, driven in part by geography, tradition, and beliefs[5,10] despite no evidence of benefit.[2,6,11,12] We and others have underscored for the last decade that the evidence is at best neutral because it does not show clear, worse outcomes for seizure prophylaxis.[2,12] The essential problem in this debate is that the evidence we cite is undercut by study bias: unclear allocation methods, vague description or no use of blinding, little or imprecise use of sample size calculations, and, crucial for this case, tumor selection.

Risk of bias.—Bias is any systematic distortion of the true effect of an intervention on outcomes of interest. This deviation can be in favor of or against the intervention we want to test, and it can be unintentional or purposeful. We can now grade risk of bias in research with valid tools in continuous development and refinement.[13,14] Our perception of risk of bias can change in time; a reassessment of bias while updating a systematic review found that bias risk was higher than estimated initially when the goal was to expose the flaws of seizure prophylaxis. The relevant causes of systematic error were inadequate description of the randomization method, lack of or insufficient blinding, and no stipulation of sample size or an underpowered study when a sample size was estimated.[15,16]

Patient selection.—Tumor selection is a decisive factor affecting clinical heterogeneity. Terms such as *brain tumor*, *primary brain tumor*, and *intracranial tumor* are noninformative in discussions about tumor-related epilepsy. It is no longer methodologically appropriate to include different neoplastic and nonneoplastic diseases, or different tumor types, into a single trial and generalize its conclusions. We have been generalizing all these years without a careful case-by-case evaluation. All trials of seizure prophylaxis included participants with different tumor types. The glioma category was not classified in detail except in 1 study in which there were 4 patients with

low-grade glioma in the treatment arm, and none had oligodendroglioma. A study with good methodological quality had only 4 patients with glioma as controls, and none in the intervention arm.[6] In summary, one of the tumor types with a high rate of seizures (oligodendrogliomas, the diagnosis of our patient), was not represented in the systematic reviews.

Our knowledge of glial epileptogenesis has improved to understand now that gliomas with *IDH* 1 or 2 mutations carry a very high risk of epileptic seizures.[17–19] Many of these neoplasms are in the frontal and temporal lobes, infiltrating the cortex as seen on T2/fluid-attenuation inversion recovery MRI sequences. The odds of an epileptic seizure in this case may still be high despite the possibility of seizure control after surgery, irradiation, or chemotherapy.[20]

Position: Discontinue Antiepileptic Prophylaxis—Reply

Drs Nagpal, Hixson, and Stocksdale

We appreciate our counterparts' critique of the studies examining the use of AED prophylaxis in this patient population and acknowledge that there are weaknesses in the designs of many of the studies cited. However, as our colleagues also note, there is simply no evidence supporting a benefit from continuing AED treatment for the patient featured in the vignette. Additionally, despite some methodological concerns for individual studies, the growing literature from multiple angles actually points to a lack of benefit.

Additionally, there are consequences to ongoing AED treatments that have not yet been fully discussed. At the time of the original AAN guidelines, all the primary studies compared first-generation AEDs (phenytoin, phenobarbital, or valproic acid) to a control intervention. These agents have many undesirable effects, including constitutional symptoms, cognitive deficits, hepatotoxicity, and the rare but life-threatening Stevens-Johnson syndrome. They are especially problematic in patients with gliomas due to interactions with chemotherapy and glucocorticoids via the induction of hepatic enzymes and protein binding.[6] A later Cochrane systematic review of the same 4 RCTs analyzed in the AAN-endorsed meta-analysis revealed a number needed to harm of 3 in the pooled AED groups treated with a first-generation AED.[2] Given the improved tolerability and general efficacy of second-generation AEDs, including levetiracetam, many providers who prescribe prophylactic AEDs have updated their preferred agent both in the perioperative and long-term settings. Two surveys of AANS-affiliated neurosurgeons showed a shift in the preferred AED among those who prescribe prophylaxis from 96% phenytoin in 2005 to 85% levetiracetam in 2017.[5,21]

No RCTs evaluating the efficacy of second-generation AEDs to prevent or delay the occurrence of a first seizure in brain tumor patients compared to placebo or no prophylaxis have been completed. Many studies of second-generation AEDs are severely limited by their heterogeneous AED groups that include patients treated with phenytoin or levetiracetam, confounding any isolated effect of levetiracetam.[22] Given that prophylaxis with phenytoin was not recommended by the AAN guidelines, the most relevant study would compare a single second-generation AED with a control (placebo or no treatment) rather than a first-generation AED. Three retrospective studies comprising 402 patients have both compared a majority second-generation AED group (all >50% levetiracetam) to no prophylaxis and excluded patients with a history of seizures prior to surgery.[9,23,24] Two of these studies included only patients with high-grade glioma, one exclusively involving patients with glioblastoma and the other involving both glioblastoma and World Health Organization grade III gliomas without further description of histologic subtypes (ie, anaplastic astrocytoma vs anaplastic oligodendroglioma).[9,24] The third study included patients with a variety of intra-axial brain tumors, with the most common tumor type being metastatic disease.[23] None of these studies showed a significant reduction in seizure risk in the prophylaxis group compared to no AED. A recent Brain Tumor Trials Cooperative placebo-controlled RCT of long-term prophylactic lacosamide (another second-generation AED) was terminated after accruing 37 of a planned 302 patients in 4 years (NCT01432171).

Tumor-associated epileptogenesis is incompletely understood, but likely occurs in part via unique mechanisms that may explain the inability of classic AEDs to prevent its onset. Increased extracellular glutamate has been shown to be associated with seizures in glioma patients.[25] Upregulation of the cysteine/glutamate transporter X_C^- that removes glutamate from the tumor cell coupled with decreased reuptake of glutamate via the downregulated astrocytic membrane excitatory amino acid transporter both contribute to elevated extracellular glutamate. As our colleagues mentioned, *IDH* 1 or 2 mutations have also been associated with increased seizure risk, possibly due to glutamatergic effects of 2-hydroxyglutarate. This increased risk, however, has been demonstrated only *preoperatively* and its use as a predictor of postoperative seizure risk (and potentially increased benefit of long-term prophylaxis) remains unclear.[26] Most AEDs, including levetiracetam, do not act directly on the glutamatergic system and may therefore be ill equipped to prevent tumor-associated epilepsy. Further, some late-onset tumor-associated seizures may be due to tumor progression with a mechanism that differs from the epileptogenic effect of a static tumor.[1,23]

More studies in the era of second-generation AEDs are needed to investigate the role of long-term AED prophylaxis in patients with brain tumors.[9,23,24] Currently, however, there is no conclusive evidence, prospective or otherwise, that AEDs prevent or delay the onset of first seizure. Despite the improved tolerability of second-generation AEDs, their use is not without consequence. Levetiracetam, the most commonly used agent, is associated with significant cognitive, behavioral, and psychiatric effects that can impair quality of life.[27] Future prospective studies should first attempt to demonstrate a benefit to prophylaxis over placebo prior to using another AED as a comparator. Until we have this evidence that AED prophylaxis effectively prevents or reduces the severity of tumor-associated seizures with an acceptable toxicity profile, the

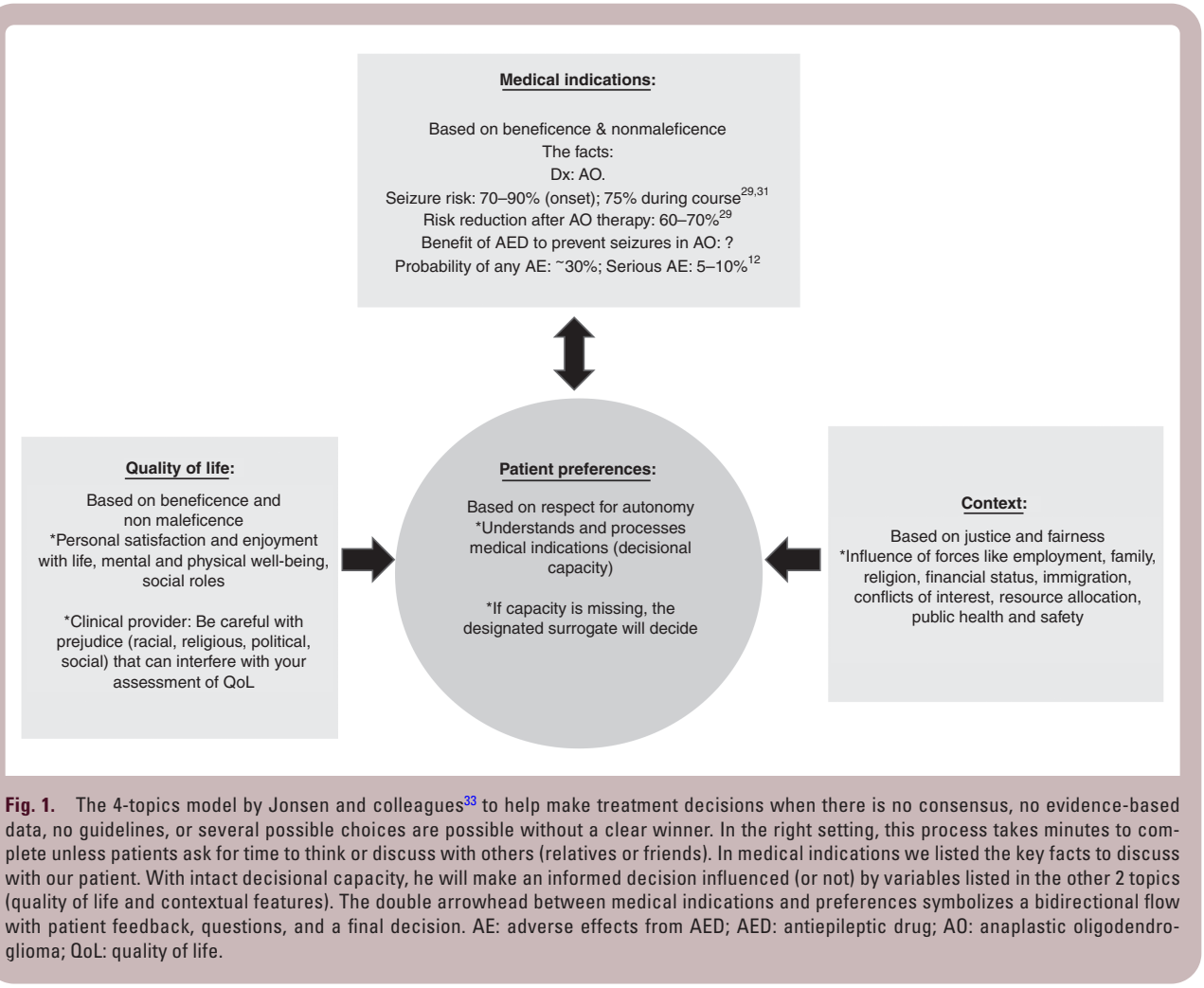

Fig. 1. The 4-topics model by Jonsen and colleagues[33] to help make treatment decisions when there is no consensus, no evidence-based data, no guidelines, or several possible choices are possible without a clear winner. In the right setting, this process takes minutes to complete unless patients ask for time to think or discuss with others (relatives or friends). In medical indications we listed the key facts to discuss with our patient. With intact decisional capacity, he will make an informed decision influenced (or not) by variables listed in the other 2 topics (quality of life and contextual features). The double arrowhead between medical indications and preferences symbolizes a bidirectional flow with patient feedback, questions, and a final decision. AE: adverse effects from AED; AED: antiepileptic drug; AO: anaplastic oligodendroglioma; QoL: quality of life.

prophylactic use of AEDs in patients with brain tumors is not indicated.

Position: Continue Long-Term Seizure Prophylaxis—Reply

Drs Shivaprasad, Rai, and Tremont-Lukats

We find common ground with Nagpal and associates in fundamental areas. First, that current evidence for seizure prophylaxis is minimal and faulty. We also regret the scant information on adverse events associated with AEDs from many of the trials. Second, the generational shift in AED choice is not surprising, considering the real problem of interaction with chemotherapy and the adverse effect profile of older AEDs. Nonetheless, we cannot forget that reliance on older AEDs will continue worldwide because many countries do not have easy access to phenobarbital, phenytoin, valproate sodium, or carbamazepine, let alone newer AEDs.[28] Nagpal and her associates also proposed that therapeutic inertia or unwillingness to deprescribe (a problem in patients on polypharmacy) account for the reticence in discontinuing AED prophylaxis. This argument is an unproven yet provocative hypothesis worth testing in a future study.

We agree that high-grade astrocytomas, leptomeningeal metastases, meningiomas, and most brain metastases do not require long-term prophylaxis. Our 40-year-old man with proven anaplastic oligodendroglioma is not in any of those groups. Diffuse and anaplastic oligodendrogliomas have an unacceptably high seizure rate of 70% to 91% at diagnosis,[29–32] and nearly 77% during the disease course.[31] Surgery, irradiation, and chemotherapy can each contribute to seizure control, but 30% to 44% of these patients remain with refractory epileptic seizures,[29] and about 50% will have seizure control that can be total, partial unsatisfactory, or partial satisfactory.

We identify here an ethical conflict: Will AED prophylaxis prevent seizures (beneficence) with an acceptable tradeoff of adverse effects (nonmaleficence) despite no supporting evidence? We propose a solution based on a method to solve conflicts in clinical ethics, the 4 topics or the "4-box" model.[33] The first topic (medical indications), specifies the problem, the treatment goals, benefits, and risks. The second topic (patient preferences), entails an open discussion of medical indications with a patient capable of decision making or with surrogates if not. The underpinning of the second topic is the principle of respect for the

patient's autonomy. Topics 3 (quality of life) and 4 (contextual features) will shape and provide arguments for our patient to justify his decision. As an exercise, we applied the 4 topics to our patient (Figure 1). The 4-topics model is only one approach to resolve a situation with no clear or straightforward answer. As with every methodology, it has its shortcomings and may not apply to every clinical dilemma. In the absence of credible evidence such as in this case, an informed decision driven by the principle of patient autonomy may be the most equitable solution.

Discussion

Both sides of this debate agree on several salient facts: that seizures are relatively common in patients with glioma, that seizures contribute to comorbidity, and most important that the currently available evidence does not allow for definitive determination of the role of long-term prophylactic use of contemporary AEDs in this important patient population. In this light, it might seem that a double-blinded randomized trial to assess the efficacy of long-term prophylactic AED therapy would be embraced by the neuro-oncology community, but unfortunately this has not been the case to date. For example, NCT01432171, a trial of lacosamide vs placebo, opened in 2012 with an anticipated enrollment of up to 302 patients, but was terminated in 2018 having enrolled only 37 patients. Hopefully this situation will change with the ongoing Seizure PRophylaxis IN Glioma (SPRING) trial being conducted in the United Kingdom. In this multicenter phase III study, 804 subjects with suspected glioma will be randomized 1:1 to levetiracetam or no AED prior to surgery, and treatment will be continued for up to one year. The primary end point will be one-year risk of first seizure, with secondary end points including time to first seizure and various quality of life outcomes.[34] While awaiting the results of this study, neuro-oncologists will have to continue to evaluate the specific seizure risk profile of each patient, considering factors such as tumor location, glioma subtype, and perceived likelihood of antiepileptic toxicity, and act accordingly. The authors hope that this discussion will aid them in this effort.

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