Optimizing antiseizure medication treatment in glioma patients with epilepsy

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CHAPTER 1

General introduction and outline

Gliomas

In 1926 the book '*A classification of the Tumours of the Glioma Group on a Histogenetic Basis with a correlated Study of Prognosis*' was published by the well-known physician Harvey Cushing and his protégé Percival Bailey, which laid the foundation of brain tumor grading of modern-day neuro-oncology. Virtually all brain tumors were called gliomas during this time, but based on the pathological material of 414 glioma cases Bailey classified these tumors into 13 separate categories. In 1927 overall survival time was related to tumor type and the classification was reduced to 10 categories, with oligodendroglioma and astrocytoma already being separate subtypes.[1] About 50 years later, in 1979, the World Health Organization (WHO) published the classification of tumors of the nervous system. In 1993, 2000, 2007, 2016, and 2021 subsequent editions of the WHO classification of tumors of the central nervous system have been published, which until 2016 relied primarily on histology. Since 2016, molecular parameters were used in addition to histology to define brain tumor entities.[2] Molecular parameters include isocitrate dehydrogenase (IDH) mutations and 1p/19q codeletion which correspond to increased overall survival times, due to their inherent slow growth rate and better response to antitumor treatment.[3]

Gliomas are graded according to the specifics of each entity and their expected natural history, ranging from WHO grade 1 to 4, with grade 1 gliomas generally occurring in children and being frequently curable if surgically removed, up to grade 4 gliomas as highly malignant tumors with a relatively poor prognosis.[2] Gliomas account for 80% of all malignant primary central nervous system tumors, with an incidence of ~5 per 100.000 person-years, and glioblastoma comprising 57% of all gliomas.[4, 5] Median overall survival time in glioma ranges widely, from 15 months in glioblastoma, IDH-wildtype, up to 13 years in astrocytoma, IDH-mutant, WHO grade 2, and oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, grade 2, after antitumor treatment (i.e. surgical resection, chemotherapy, and radiotherapy).[6, 7] Generally, glioma patients suffer from a wide range of symptoms, most of neurological origin (e.g., neurocognitive deficits, motor weakness, dysphasia, and headache). Epileptic seizures are the most prevalent symptom throughout the total disease trajectory in patients with glioma,[8] often representing the first clinical sign in patients with a low-grade glioma.

Epilepsy in glioma

The conceptual definition of an epileptic seizure is as follows: 'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.' The occurrence of epileptic seizures has been documented for >4000 years and descriptions of epileptic seizures have been found among others on Akkadian tablets,

ancient Egyptian papyrus, ancient Chinese and Greek texts.[9] Arguably, the most famous political leader who appeared to have suffered from epileptic seizures is Julius Caesar (c.100 - c.44 B.C.). A hypothesis is that his late onset epileptic seizures were due to a low-grade glioma. Despite probably having intracranial pathology, Caesar died of a competing risk, he was assassinated by a group of senators ending his rule as Emperor of the Roman Republic.[10] Hippocrates of Kos (c.460 - c.370 B.C.) was among the first to attribute the occurrence of epileptic seizures to the brain instead of a metaphysical cause.[9, 11] The discussion of epilepsy's etiology, physiologic versus metaphysical, continued until the Enlightenment period in the 18th century when Europe's medical community stood in almost complete unison against a metaphysical etiology of epilepsy.[10]

Epilepsy, as defined by the International League Against Epilepsy (ILAE), is a brain disorder characterized by an enduring predisposition to generate epileptic seizures and the consequences (neurobiological, neurocognitive, psychological, and social) of this condition. According to the ILAE proposed practical clinical definition, a patient is considered to have epilepsy by meeting any of the following conditions: 1) ≥2 unprovoked (or reflex) seizures occurring >24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (≥60%) after two unprovoked seizures, occurring over the next 10 years; or 3) diagnosis of an epilepsy syndrome.[12] Usually in clinical practice in glioma patients the diagnosis of epilepsy is made after the occurrence of one epileptic seizure. The incidence differs between glioma types and the (preoperative) incidence of seizures is generally higher in low-grade (e.g., ~75% for astrocytoma, IDH-mutant, grade 2, and oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, grade 2) compared to high-grade gliomas (e.g., ~25% for glioblastoma, IDH-wildtype).[13] IDH-mutation and D-2-hydroxyglutarate (i.e., an active glutamate metabolite produced by IDH-mutation) are important contributing factors to epileptogenesis, which is defined as the development and extension of brain tissue capable of generating spontaneous recurrent epileptic seizures.[14, 15] As mentioned earlier, epilepsy is a brain disorder, which translates in glioma patients to a negative effect on social and economic participation, decreased level of health-related quality of life (HRQoL), and impairments in neurocognitive functioning. As a consequence, achieving (enduring) seizure control is an important treatment goal and of paramount importance.[16, 17] Antitumor treatment including surgery, radiotherapy, and chemotherapy have demonstrated a beneficial effect on seizure control in glioma patients, but usually antiseizure medication (ASM) treatment is highly recommended after a first seizure has occurred, because of the high risk of a recurrent seizure.[18-20] Of note, throughout this thesis the terms antiepileptic drug (AED) and ASM are used interchangeably. More recently, ASM has replaced the term AED, because there is currently no evidence these agents alter the disease course of epilepsy and provide symptomatic treatment only.[21]

Antiseizure medication treatment

The goal of ASMs is to prevent or suppress the generation, propagation, and severity of epileptic seizures.[21] Bromide was the first ASM introduced in 1857 (Table 1) for the treatment of epilepsy and famously prescribed to Vincent van Gogh (1853 - 1890), which resulted in relief of his seizures,[22, 23] although it is disputed whether he truly suffered from epilepsy.[24] In the following decades ASMs such as phenytoin, carbamazepine, and valproic acid were introduced. Many of these first-generation ASMs were strong hepatic enzyme-inducers or -inhibitors, meaning they posed a high risk for drug-drug interactions.[25] In the 1990s the second-generation ASMs emerged, with the introduction of ASMs with different mechanisms of action (e.g., levetiracetam which primary mechanism of action is inhibition of glutamate release by binding to synaptic vesicle SV2A protein) and more favorable pharmacokinetics.[26] Many of these second-generation ASMs exhibited limited to no drug-drug interactions and therefore were thought to have less (intolerable) adverse effects.[27] In the 2000s the third-generation ASMs came up with the introduction of lacosamide and subsequently a large number of other ASMs, including brivaracetam, eslicarbazepine, and perampanel.[25, 28] These ASMs are regarded as the third-generation, because some of them represent the third-generation in drug improvement (e.g., eslicarbazepine) and others have new mechanisms of action (e.g., perampanel).[28] However, different classifications of drug-generations have been proposed.[21] Currently, ~30 ASMs have been approved in Europe, meaning the ASM market is crowded. Many of the big pharmaceutical companies previously active in the development of ASMs have withdrawn from the market, while small- and medium sized pharmaceutical companies have entered the market. These small- and medium sized pharmaceutical companies mainly develop novel ASMs for rare epileptic syndromes such as Lennox-Gastaut syndrome (rufinamide and cannabidiol) and tuberous sclerosis complex (everolimus and cannabidiol) in which unmet needs are high. To this day no specific ASM has been approved for the treatment of epilepsy in glioma patients.[21]

In 2013 the ILAE updated the current evidence on ASM efficacy in patients with epilepsy and established the following ASMs as level A class evidence: carbamazepine, levetiracetam, phenytoin, and zonisamide for adults with focal onset seizures, gabapentine and lamotrigine for elderly with focal onset seizures. For adults with generalized onset tonic-clonic seizures only, level C class evidence was established for the following ASMs: carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproic acid.[29] According to the ILAE the primary outcome in studies evaluating ASMs for epilepsy should be efficacy or effectiveness, ideally evaluated after a minimum of 24- or 48-weeks of treatment, respectively.[29] In the glioma population, studies evaluating ASMs for epilepsy most commonly use 3, 6, or 12 months of treatment, in line with standard clinical follow-up appointments. In glioblastoma patients, evaluating ASM primary outcome at 3 months seems appropriate due to the limited overall survival time. Efficacy refers to the ability of

Table 1. Antiseizure medications through the decades and their proposed mechanism(s) of action

Antiseizure medication[21, 62, 63]	Year of approval*	Proposed (primary) mechanism of action
First-generation		
Potassium bromide	1857	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Phenobarbital	1912	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Phenytoin	1938	Na^+ channel blockade
Mephobarbital	1945	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Trimethadione	1946	T-type Ca^{2+} channel blockade
Mephenytoin	1946	Na^+ channel blockade
Paramethadione	1949	T-type Ca^{2+} channel blockade
Phenacemide	1951	Multiple (Na^+ channel blockade, Ca^{2+} channel blockade)
Adrenocorticotropic hormone (ACTH)	1952	Inducing steroid release
Phensuximide	1953	Unclear
Acetazolamide	1953	Accumulation of carbonic acid by inhibition of carbonic anhydrase
Primidone	1954	GABA potentiation
Ethotoin	1957	Na^+ channel blockade
Methsuximide	1957	T-type Ca^{2+} channel blockade
Ethosuximide	1958	T-type Ca^{2+} channel blockade
Chlordiazepoxide	1958	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Sulthiame	1960s	Accumulation of carbonic acid by inhibition of carbonic anhydrase
Diazepam	1963	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Carbamazepine	1964	Na+ channel blockade
Valproic acid/divalproex	1967	Multiple (e.g., Na^+ channel blockade, T-type Ca^{2+} channel blockade, and GABA potentiation)
Clonazepam	1968	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Clobazam	1975	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Progabide	1985	GABA potentiation as $GABA_A$ and $GABA_B$ receptor agonist
Midazolam	1985	GABA potentiation as $GABA_A$ receptor positive allosteric modulator
Second-generation		
Vigabatrin	1989	GABA potentiation by inhibition of GABA aminotransferase
Lamotrigine	1990	Multiple (e.g., Na^+ channel blockade, Ca^{2+} channel blockade)

Table 1. Continued

Antiseizure medication[21, 62, 63]	Year of approval*	Proposed (primary) mechanism of action
Oxcarbazepine	1990	Na+ channel blockade
Felbamate	1993	Multiple (e.g., Na^+ channel blockade, Ca^{2+} channel blockade, and GABA potentiation)
Gabapentin	1993	Ca^{2+} channel blockade by binding to α2δ subunit
Topiramate	1995	Multiple (e.g., Na^+ channel blockade, Ca^{2+} channel blockade, GABA potentiation)
Fosphenytoin	1996	Na+ channel blockade
Tiagabine	1996	GABA potentiation by GABA reuptake inhibition
Levetiracetam	1999	Inhibition of glutamate by binding to synaptic vesicle SV2A protein
Zonisamide	2000	Multiple (e.g., Na^+ channel blockade, T-type Ca^{2+} channel blockade)
Stiripentol	2002	Multiple (e.g., Na^+ channel blockade, GABA potentiation)
Pregabalin	2004	Ca^{2+} channel blockade by binding to α2δ subunit
Rufinamide	2004	Na^+ channel blockade
Third-generation		
Lacosamide	2008	Na^+ channel blockade
Eslicarbazepine	2009	Na^+ channel blockade
Retigabine	2011	K^+ channel activation
Perampanel	2012	Inhibition of glutamate by binding to binding to AMPA receptor
Everolimus	2016	mTOR inhibitor
Brivaracetam	2016	Inhibition of glutamate by binding to synaptic vesicle SV2A protein
Cannabidiol	2018	Reduction of ASM-metabolism by CYP3A4-inhibition
Cenobamate	2019	Multiple (e.g., Na^+ channel blockade, GABA potentiation as $GABA_A$ receptor positive allosteric modulator)
Fenfluramine	2020	Unclear

*Year in which the drug was first approved in the United States of America or Europa. In case of absence of Food and Drug Administration (FDA) or European Medicines Agency (EMA) approval the mentioned year corresponds to introduction to the market/scientific community.

an ASM to achieve a reduction in seizure frequency (e.g., seizure freedom [Figure 1]). Tolerability refers to the incidence, severity, and impact of ASM-related adverse effects. The effectiveness of an ASM encompasses both efficacy and tolerability. A measure for effectiveness is ASM treatment failure, defined as the percentage of patients discontinuing the prescribed ASM treatment at the end of a specified period due to uncontrolled seizures, intolerable adverse effects or other reasons.[30, 31] Little is known about the comparative efficacy and effectiveness of ASMs in glioma patients and comprehensive data on efficacy

EFFICACY = The ability of an ASM to achieve a reduction in seizure frequency. Examples of outcome measures assessing ASM efficacy:

- Time to first seizure
- ≥50% seizure reduction
- Seizure freedom

TOLERABILITY = The incidence, severity, and impact of ASM-related adverse effects. Examples of outcome measures assessing ASM tolerability:

- (Serious) adverse events
- Neurocognitive functioning
- Depressive symptoms

EFFECTIVENESS = Both efficacy and tolerability. Examples of outcome measures assessing antiseizure medication (ASM) effectiveness:

- ASM retention rate
- Time to ASM treatment failure

Figure 1. Efficacy and tolerability are two sides of the same denarius (coin), while effectiveness is the denarius.

and effectiveness of ASM treatment in glioma patients are lacking, complicating ASM treatment decisions for healthcare professionals. In studies evaluating the efficacy of ASMs in glioma patients methodological considerations, such as death as competing risk, have insufficiently been taken into account, thereby complicating interpretation of results.[32, 33] First-line monotherapy valproic acid in glioma patients was preferred up to a decade ago and gained increased attention due to its supposed antitumoral properties as a histone deacetylase inhibitor besides its efficacy for seizure control,[32-34] but improved overall survival could not be demonstrated in a meta-analysis of prospective trials.[35] In later years, first-line monotherapy levetiracetam became more preferred in glioma patients,[36, 37] as this ASM has several advantages including a lack of hepatic metabolism and a wide therapeutic index.[38] However, the effectiveness of levetiracetam versus valproic acid has insufficiently been investigated in glioma patients. Both levetiracetam and valproic acid are non-enzyme-inducing ASMs (non-EIASMs). EIASMs (e.g., phenytoin and carbamazepine) are discouraged by guidelines of the European Association for Neuro-Oncology (EANO), due

to its potential to interact with chemotherapeutic agents.[18, 39] However, the majority of glioma patients do not receive systematic therapies that are affected by EIASMs (e.g., temozolomide).[40] This recommendation therefore might be too strict and it may be possible that first-line EIASMs are more effective than the commonly prescribed non-EIASM levetiracetam. Thus, also this remains to be investigated.

Unfortunately, about a third of (non-)brain tumor-related epilepsy patients do not achieve seizure freedom on a single ASM and need an add-on ASM.[41, 42] According to the ILAE, drug-resistant epilepsy is defined as: 'A failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.'[43] It is already challenging to find the optimal first-line ASM treatment, thus finding the optimal duo- or triple therapy with >400 duo- and >4000 triple therapy combinations is arduous. How to rationalize prescription of combinations that provide the best possibility of optimal seizure reduction? The ideal ASM combination demonstrates pharmacological synergism, which can be either better efficacy with similar tolerability, better tolerability with similar efficacy, or better efficacy and tolerability.[44] A proposed hypothesis is rational polytherapy: the process of selecting ASM combinations with different mechanisms of action, as it is supposed to be more effective than polytherapy with similar mechanisms of action.[45] The concept of pharmacological synergism with ASM combination therapy is not new. Neurologist William Gowers was in the 19th century already convinced that combinations of bromide with other drugs resulted in a greater efficacy than monotherapy.[44] In preclinical studies using male audiogenic susceptible mice the efficacy of the ASM combination therapy of levetiracetam with valproic acid surpassed all other evaluated ASM combinations. The potency (i.e., the dose to protect 50% of animals against clonic seizures) of valproic acid combined with levetiracetam increased 28-fold compared to valproic acid alone and the therapeutic index (i.e., the ratio between the median toxic dose and the median effective dose) dramatically increased when combining levetiracetam with valproic acid. This indicates a possible synergistic effect for this ASM combination of two ASMs with different mechanisms of action.[46] Levetiracetam's supposed primary mechanism of action is through binding to synaptic vesicle glycoprotein 2A (SV2A) through which it exerts its anticonvulsant properties,[47] while valproic acid has multiple mechanisms of action including blockade of voltage-dependent natrium channels and GABAergic potentiation. Synergistic effect of levetiracetam with valproic acid might be due to combining different mechanisms of action and/or due to their shared effect on synaptic vesicle release (through SV2A and T-type calcium channel inhibition, respectively). [46, 48] However, truly convincing (clinical) evidence is still lacking and rational polytherapy remains controversial. Given the substantial rate of ASM polytherapy use (about a third in both non-brain tumor-related epilepsy [BTRE] and glioma patients with epilepsy)[41, 42] and the lack of high-quality comparative effectiveness studies, studies comparing existing ASMs and investigating potentially more effective medical treatment options in glioma patients with epilepsy are warranted.

The tolerability of ASMs is integral to successful treatment as adverse effects are a leading cause of treatment failure with ASMs and result in early discontinuation in up to 25% of in patients with epilepsy. An adverse effect is an undesired harmful effect that can be attributed, directly or indirectly, to the ASM.[49] Tolerability of ASMs is complicated in glioma patients as most patients receive multimodal treatment with surgical resection, radiotherapy, systemic therapy, corticosteroids, and other concomitant medications all potentially causing adverse drug effects, which may be similar to the adverse drug effects caused by ASMs. For example, the highly prevalent symptom fatigue in glioma patients could be caused by any of the previously mentioned treatments.[50] Evaluating causality for adverse drug effects in order to know whether a change in the ASM treatment regimen is necessitated is of importance and the Naranjo scale can assist in this process.[51] The Naranjo scale is a 10-item questionnaire and the higher the score, the more likely it is that the adverse reaction was caused by the suspected drug. Each ASM has its own toxicity profile. Valproic acid has been associated with decreased neurocognitive functioning and thrombocytopenia,[16, 52, 53] which can be worsened in combination with the chemotherapeutic agent temozolomide. On the contrary, due to its mood-stabilizing properties it generally causes no psychiatric adverse effects.[54] Arguably, levetiracetam has an opposite toxicity profile. Initially, levetiracetam was postulated to have mood-stabilizing and anxiolytic properties, but this could not be demonstrated in two randomized, double-blind, placebo-controlled trials in patients with bipolar disorder and generalized social anxiety disorder, respectively.[55] By contrast, it is now known for its potential (severe) psychiatric adverse effects (e.g., anxiety, agitation, and depression),[56] but has been associated with improved neurocognitive functioning and generally no thrombocytopenia.[57, 58] The psychiatric adverse effects might ameliorate with an add-on ASM, such as lamotrigine, likely due to its mood stabilizing properties.[41] This might apply to valproic acid as well, making it a rational choice to combine with levetiracetam. To what extent the psychiatric and neurocognitive side effects of ASMs, specifically valproic acid and levetiracetam, compare to each other in glioma patients is currently unknown.

Both efficacy and tolerability are important drug properties in ASM treatment selection. However, other drug properties such as ease of administration and titration rate, mode of clearance, and drug-drug interactions should not be overlooked when selecting an ASM and become especially important when combining ASMs.[41] Among ASMs, benzodiazepines (e.g., clobazam) are easy to administer and make them an useful add-on ASM to a polytherapy treatment regimen.[59] Despite the discouragement by guidelines to avoid prescribing EIASMs in glioma patients, they still seem to be frequently prescribed.[40] In addition, European guidelines recommend against routinely prescribing prophylactic ASM treatment in brain tumor patients,[18] but this is a hotly debated topic.[60] The same applies to the withdrawal of ASMs. Recently, it has been demonstrated in a prospectively designed ASM withdrawal study that ASM withdrawal can be considered in carefully selected glioma

patients with stable disease and long-term seizure freedom.[61] However, attitudes of neuro-oncology professionals with regard to ASM withdrawal and to which extent the reduction of ASMs and dosage is considered is unknown. Due to the lack of high-quality comparative efficacy and effectiveness studies in particular, ASM prescribing behavior and treatment policy seems to differ considerably between physicians treating glioma patients with epilepsy. It is important to gain more insight in ASM prescribing behavior and treatment policy, as this is the first step in a more uniform ASM treatment policy in glioma patients internationally, according to the highest scientific evidence.

Aims and outline of this thesis

Part 1. Antiseizure medication efficacy

Over the past decades numerous studies have been conducted with regard to the efficacy of ASMs in glioma patients. However, a comprehensive overview of the conducted studies and comparative efficacy studies taking into account important methodological considerations in this research area were missing. In **chapter 2**, a systematic review with regard to the efficacy of ASMs in glioma patients with epilepsy is described. In **chapter 3** two of the most commonly prescribed first-line monotherapy ASMs in glioma, levetiracetam and valproic acid, are compared regarding efficacy and tolerability. **Chapter 4** compares first-line monotherapy levetiracetam with by guidelines generally discouraged monotherapy EIASMs. Unfortunately, a considerable number of patients have insufficient seizure control on ASM monotherapy and thus need ASM polytherapy. In **chapter 5** the effectiveness of ASM dual therapy is evaluated, comparing levetiracetam combined with valproic acid versus dual therapy combinations with either levetiracetam or valproic acid and another ASM. Still, a number of patients have uncontrolled seizures on ASM dual therapy and are prescribed ASM triple therapy. In **chapter 6** the effectiveness of ASM triple therapy is reported, evaluating levetiracetam combined with valproic acid and clobazam versus other triple therapy combinations. Lastly, two frequently prescribed add-on ASMs in glioma patients are the second-generation ASM lamotrigine and the third-generation ASM lacosamide. However, the comparative effectiveness between these two ASMs in glioma patients has not been studied yet. Therefore, in **chapter 7** the effectiveness of lamotrigine versus lacosamide is evaluated.

Part 2. Antiseizure medication tolerability

Efficacy and tolerability constitute two sides of the same coin in achieving successful treatment. Both neurocognitive deficits and psychiatric symptoms are frequently occurring in glioma patients, due to a large number of potential factors. Some of these factors might be difficult to adjust (e.g., the disease itself despite antitumor treatment), but others might

be more easy to adapt by a physician, such as the choice of ASM treatment. Given a large number of glioma patients are prescribed levetiracetam and valproic acid, both with the potential to cause and alleviate neuropsychiatric adverse effects, **chapter 8** assesses the effect of ASMs (as monotherapy and as polytherapy and in particular levetiracetam versus valproic acid) with regard to neuropsychiatric adverse effects.

Part 3. Antiseizure medication prescription behavior and treatment policy

Several surveys have been conducted evaluating ASM prophylaxis patterns in seizure-naïve brain tumor patients and showed clinical practice differences between specialties and countries. However, it is unknown how physicians deal with the lack of high quality comparative efficacy ASM treatment studies and ASM withdrawal studies in glioma patients, complicating management of epilepsy in this population. **Chapter 9** explores the attitudes of members of the European Association of Neuro-Oncology (EANO) on ASM prescription preferences, timing of ASM treatment, organization of epilepsy care, and ASM withdrawal in a survey.

Lastly, in **chapter 10** a summary, a general discussion on our findings, and future directions are provided.

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