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Titel | Title

Systematic Review and Medication Use Evaluation of Levetiracetam Prescriptions in the Perioperative Neurosurgical Setting

verfasst von | submitted by

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1 Introduction

Patients with cerebral hemorrhages, traumatic brain injuries, intracranial tumors or other acute medical conditions, which urge the need of an immediate neurosurgical intervention are at particular risk of experiencing an epileptic seizure. These conditions are among the most common neurological complications in the perioperative, neurosurgical setting and may be linked to several consequences (1-3). These include, for example, worsening of the patients' condition resulting in the need of increased care or even prolonged hospitalization. Considering this, therapy with antiseizure medication as an antiepileptic prophylaxis with or without experienced seizure is often prescribed in the clinical course. In this setting, prescription of the antiepileptic drug levetiracetam has become standard of care in the past years. (4)

Levetiracetam comes with a favorable pharmacodynamic profile, an immediate seizure suppressing effect and no risk of significant drug-drug interactions compared to older antiepileptic drugs. These properties therefore lead to a widespread use of levetiracetam in the neurosurgical setting, for both primary and secondary seizure prophylaxis.

Guidelines from different associations like *Deutsche Gesellschaft für Neurologie* (DGN), the European Association of Neuro-Oncology (EANO) and the American Academy of Neurology (AAN) support a selective and indication-oriented use, especially in the absence of clinical seizure.

In contrast, actual clinical practice seems to differ, as especially levetiracetam may frequently be started at admission and tends to be continued at discharge without specific reassessment recommendations. This may result in unjustified long-term prescriptions without evidence-based medical benefit and can put the patients at risk for potential side effects, such as fatigue, somnolence, or even psychiatric symptoms. (5-7)

This master thesis will address the question of levetiracetam prescriptions in the perioperative neurosurgical setting in patients without epilepsy for primary and secondary seizure prevention.

First, a systematic literature review will summarize available evidence for prescribing levetiracetam in patients with or without experienced seizure in the perioperative neurosurgical setting which will be complemented by relevant guideline recommendations. Based on these findings, criteria for primary and secondary seizure prophylaxis with levetiracetam will be generated. Second, a retrospective medication use evaluation will be performed to assess the alignment of levetiracetam prescriptions with the synthesized criteria.

The idea for this thesis topic emerged from the established practice of clinical pharmacy services at the Department of Neurosurgery at the Vienna General Hospital. At this hospital,

clinical pharmacists are not only involved in review of the patients medication during their inpatient stay at the neurosurgical wards, but also actively participating in interdisciplinary ward rounds with other healthcare professionals such as surgeons, ward physicians, nursing staff, clinical psychologists, physiotherapists and speech and language therapists. As part of the clinical involvement, clinical pharmacists are committed to identifying and managing drug related problems and promoting evidence-based use of medications.
Within this context, the use of levetiracetam emerged as a particularly important topic with its frequent application in neurosurgical patients and the ongoing discussion regarding its evidence in the perioperative neurosurgical setting.

2 Background

Neurosurgical procedures treat heterogenous pathologies affecting the central nervous system. These pathologies may derive from traumatic as well as from non-traumatic etiology, with indications for interventions often depending on the condition's severity. The most common indications for neurosurgical interventions are traumatic brain injuries (TBI), including various forms of intracranial hemorrhage such as subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH) and intracerebral hemorrhage (ICH). These hemorrhages may also arise from vascular abnormalities, such as arteriovenous malformation (AVM) or ruptured aneurysm of a cerebral artery. Moreover, brain tumors, both primary and secondary, may also require neurosurgical management.

2.1.1 Traumatic Brain Injury

Traumatic brain injury (TBI) is induced by an external force and can be caused by a forceful bump, blow, twitch to the body or head, or by an object penetrating the skull and entering the brain.(8)

Falls, traffic accidents and assault are the most common causes of TBI.(9) As TBI is heterogeneous, it can be classified in various ways including the type, mechanism of injury and its physiological response to injury, location and severity.(10)

The damage and severity resulting from TBI can be focal, which means that the damage is restricted to one area of the brain, or diffuse, affecting more than one area of the brain.(9)

Although TBI is a broad term, including a vast range of injuries, there are two broad types of brain injuries defined. The first one is penetrating TBI (also known as open TBI) resulting from an object or bone fragment piercing the skull and further entering the brain tissue. The second type of TBI is categorized as non-penetrating TBI (also known as closed head injury or blunt TBI). This is provoked by an external force which is strong enough to affect the brain within the skull.(10) Nevertheless, some accidents or trauma can cause both, penetrating and non-penetrating TBI in the same individual. Additionally, the term primary TBI, which refers to a sudden and severe injury to the brain occurring immediately upon impact, is used to characterize the initial injury. In contrast, secondary TBI is referring to the evolving changes over time deriving from primary TBI.(10, 11)

As already mentioned, TBI is heterogeneous, and most classification systems are based on patient symptoms. Therefore, mild, moderate and severe TBI are differentiated through clinical examination according to the respective symptoms. The Glasgow Coma Scale (GCS) score is a validated tool used to evaluate the level of consciousness and to grade the severity of the brain injury, with categories of mild (GCS 13-15), moderate (GCS 9-12)

or severe (GCS < 8) with regard to the patient's best motor, verbal and eye opening response.(9)

2.1.2 Subarachnoidal Hermorrhage

Subarachnoidal hemorrhages (SAH) have common symptoms, regardless of their etiology, such as severe headache with a sudden onset. The pain often emits to the neck and can be accompanied by nausea, emesis and photophobia. Furthermore, symptoms of raised intracranial pressure and meningism are also commonly witnessed in affected patients. In contrast the accompanied focal neurological symptoms depend on the origin of the hemorrhage and involvement of brain parenchyma. Common symptoms, amongst others, are epileptic seizures.(12) Generally, these patients should rapidly undergo cerebral imaging and, if required, further diagnostics, such as lumbar puncture and angiography.(13)
Subarachnoid hemorrhages develop in vessels located in the subarachnoid space, located at the base of the brain just inside the skull. Cerebrovascular aneurysms are the most common cause of spontaneous SAH with approximately 80% resulting from aneurysm rupture.(13)
An aneurysm is defined as a pathological, constant enlargement in the lumen or the ballooning of a blood vessel, resulting from the weakening of the inner muscular layer of the vessel wall.
Several additional factors such as genetics, inflammation, smoking or high blood pressure increasingly weaken the vessels walls and may result in dilating aneurysms.(14)
Not only the size of the aneurysm but also its growth rate increases the risk of rupture. In many cases neurosurgical intervention is indicated if an aneurysm is detected but this topic is beyond scope of this work.

2.1.3 Subdural Hematoma

Subdural hematomas (SDH) can be grouped into acute, subacute, and chronic types depending on the onset of clinical symptoms and imaging results.(15)
Generally, SDH refers to a form of intracranial hemorrhage characterized by abnormal accumulation of blood between the dura mater and the arachnoid membrane of the brain, caused by damage and rupture of bridging veins.(16) As a result, blood effuses from the affected vessel and forms a blood clot, hematoma. This can lead to a critical neurological emergency, which is associated with significant morbidity and mortality if not recognized and treated on time.(16)
The causes of SDH are diverse, but most often a result of trauma or coagulopathies. Spontaneous coagulopathies may lead to SDH, especially in elderly people and patients who are treated with anticoagulant therapy.(15, 17)

Nevertheless, SDH presents a diagnostic challenge, as clinical symptoms vary widely e.g., decreased consciousness, seizure and signs of increased intracranial pressure.(15-17) Although the area between dura mater and arachnoidea mater is limited, it can accommodate small blood volumes which, if increased beyond a certain point, can exert mass effect raising, intracranial pressure. This phenomenon occurs when brain tissue or structure are compressed and injured due to trauma, resulting in leakage of blood, cerebrospinal fluid or edema. Additionally, the rate of bleeding, the affected brain area and size of the hematoma have an impact on the severity of the SDH. Acute SDH, which is most commonly caused by severe impact head trauma, does often lead to emergent surgical treatment due to the rapid increase of intracranial pressure and neurologic impairment of the affected individual.(15)

In contrast chronic SDH evolves over a period of time, often over weeks, and is predominantly observed in elder patients, especially with cerebral atrophy or anticoagulant or antiplatelet medication.(15)

2.1.4 Intraparenchymal Hemorrhage

Intraparenchymal hemorrhage (IPH), also referred to as intracerebral hemorrhage (ICH) is a type of stroke caused by bleeding into the brain tissue. This accounts for around 10-20% of all strokes and is associated with a much higher morbidity and mortality than ischemic stroke.(18) A fulminant accumulation of blood in the brain parenchyma leads to increased intracranial pressure, damage of brain tissue and is often accompanied by rapid neurological worsening.

IPH can result from vast underlying causes, often classified into primary and secondary forms:

1. Primary IPH: Primary IPH is the most common form(18) and is caused by chronic hypertension or cerebral amyloid angiopathy (CAA), a type of cerebrovascular disorder characterized by accumulated amyloid beta-peptide in small cerebral blood vessels.(19) The weakening of small blood vessels, which is a result of these conditions, lead to spontaneous ruptures of the blood vessels.

2. Secondary IPH: Secondary IPH derives from structural or vascular abnormalities, such as Arteriovenous malformations (AVM), Aneurysms, Brain tumors, Coagulopathies (e.g., platelet disorders, anticoagulant use, …), drug use or trauma.(20)

Observed symptoms of IPH vary depending on the size and location of the hemorrhage, but commonly include decreased consciousness, headache, nausea or seizures (patients with cavernous malformations or venous sinus thrombosis are at higher risk).(20) Furthermore, clinical manifestations have a rapid onset and require immediate medical evaluation and management.(20)

2.1.5 Intracranial Tumors

An intracranial tumor, also known as a brain tumor, is an abnormal mass of tissue caused by uncontrolled cell growth due to altered mechanisms of cell activity control. Brain tumors and other central nervous system (CNS) tumors are the second most common cancers in adolescents and young adults Although more than 150 different brain tumors have been documented, two main groups can be described: primary brain tumors and secondary, metastatic, brain tumors.(21)

Primary brain tumors derive from the brain tissue or the brains proximate surroundings. They can be categorized as glial, composed of glial cells which are non-neuronal cells in the CNS and peripheral nervous system (PNS), and as non-glial, developing in or on structures of the brain.(21) Besides of that, subdivision into benign or malignant is also common.(21)

According to the Central Brain Tumor Registry of the United States (CBTRUS) between 2012 and 2016 the most commonly diagnosed primary brain and other CNS tumors reported were non-malignant meningioma with 37,6% (of all tumors), followed by tumors of the pituitary gland with 16,8% and malignant glioblastoma with 14,6%. Moreover, glioblastoma count as the most frequent malignant brain and other CNS tumors.(22)

Classification and Definition of Common Intracranial Tumors:

Gliomas

Glioma, representing CNS-tumors deriving from brain parenchyma, are the second most common primary intracranial tumors.

According to the World Health Organization (WHO) Classification from 2007, gliomas are categorized based on cytogenetic origin and neuropathological criteria.(23)

Furthermore, the WHO Classification of glioma was expanded in 2016, adding particular molecular biomarkers and histologic diagnosis.(24) Therefore, a more precise characterization of the tumor entity and better prediction of the prognosis and estimation of a suitable therapy could be achieved.(25, 26)

In 2021, the WHO published the fifth edition of the WHO Classification of tumors of the CNS (WHO CNS5), pointing out more precise molecular mechanisms of tumorgenesis, clinical characteristics and imaging features of the tumor entities.(24, 27)

Glioma are not graduated after the most widely used cancer TNM staging system. (T-size/extend of the main tumor, N – involved lymph nodes, M - metastasis) The suitable grading for glioma is enabled with the WHO-grading I-IV, whereby a higher WHO-grad means a higher dedifferentiation of the tumor cells. Further details regarding glioma classification are beyond the scope of this work and are therefore not mentioned.

Metastatic Brain Tumors

Tumors that expand to the brain from a primary neoplasm, which is originally derived from other organs of the body, are referred to as metastatic brain tumors. The most important primary tumors with cerebral metastasis are presented below in descending order:
bronchial carcinoma (40-60%); breast cancer (20%); malignant melanoma (10-15%); tumors of the urogenital tract; tumors of the gastrointestinal tract and thyroid Carcinoma.(28-30)

Lymphomas

Lymphomas of the CNS are neoplastic transformations of the central nervous system lymphoid tissue. There is a primary form, where the lymphoid tissue of the CNS degenerates malignantly in the brain and/or spinal cord. Additionally, a secondary form exists, in which malignant cells from lymphoid tissue deriving from other parts of the body spread into the CNS.

Overall, it can be stated that seizures are the most common clinical symptom of both primary and secondary metastatic CNS-tumors. The seizure frequency prior to diagnosis ranges between 15%-50% and often mark the first clinical sign of a brain tumor. In contrast, between 10-30% of seizures occur later in the disease. The seizure potential itself depends on multiple factors, such as tumor type, location, or size.(21, 30-32)

2.2 Definition of an Epileptic Seizure and Epilepsy

The term epilepsy originates from the ancient Greek word 'ἐπιληψία (epilēpsia)' and refers to `fallacy´. Epilepsy is one of the most common neurological diseases(33) affecting approximately 50 million people worldwide. Nevertheless, a distinction elucidates between the symptom of `epileptic seizure´ or `seizure´ and the clinical picture of `epilepsy´.

2.2.1 Epileptic Seizures

The definition of an epileptic seizure is a usually transient, fulminating dysfunction of the central nervous system. It is understood as the phenomenology based on abnormal neuronal discharges arising in the cerebral cortex.(34) This is linked to highly synchronous and highly frequent pathological and time-limited, discharged impulses deriving from several groups of neurons. Moreover, the phenomenology varies in dependance of the originate locus. Epileptic seizures can range from experiencing absences, with a duration of just a few seconds to minutes, to seizures with convulsions of an extremity, complex movements, and reduced consciousness up to classic generalized tonic-clonic seizures with deficient consciousness.(35) In this stage the patient is in the ictal state. Most epileptic seizures present with a follow-up phase, called postictal phase, which often occurs in elderly patients. This postictal state can last for up to twenty-four hours or sometimes even more. Although neurons may not show excessive discharges in this stage, patients present with many neurological symptoms such as speech and memory disorders, paralysis, and even psychological symptoms such as depression, psychotic episodes or aggressive behavior.
Auras are commonly recognized as precursors of epileptic seizures, however, they are already a constituent of the seizure or may represent the seizure itself. During auras subjective sensory perceptions are changed. Specifically, it is understood to be a limited seizure with psychological, cognitive or sensory sensations.
After cessation of the postictal state, the patient is in the interictal phase which lasts till the next seizure. The interictal state is characterized and influenced by the cause of the respective seizure which reflects the symptoms of the affected patient.(36)

Epileptic seizures, emerging for the first time, often exhibit an acute symptomatic origin. These secondary occurring seizures are temporarily associated with metabolic, toxic, traumatic, vascular, infectious, or inflammatory damage of the CNS.(37)
An acute symptomatic seizure can be synonymously understood as reactive seizure or a provoked seizure.(38) Hence, in clinical practice the use of terms is even broader. For example the terms situation related seizure, reactive seizure or acute symptomatic seizure are used.

The International League Against Epilepsy (ILAE) has proposed that these terms are synonymous and therefore should be replaced by the term acute symptomatic seizure.(37, 39)
To avoid confusion and as simplification, this work will primarily use the term acute symptomatic seizure.

Nevertheless, it is important to differentiate acute symptomatic seizure from unprovoked seizures, as they are caused by an acute systemic disturbance, such as hyponatremia, or an acute brain injury, such as cerebral hemorrhage.(37) For example, a seizure is considered as acute symptomatic if it occurs within seven days after TBI.(37, 39)

Regarding seizure recurrence, the long-term risk of seizure recurrence is lower after an acute symptomatic seizure than after an unprovoked seizure.(40) This has an impact on the decision-making whether a seizure suppressing therapy is started or not and if it is continued. In patients with an acute structural brain insult or TBI, treatment with antiseizure medication (ASM) may lower early seizure occurrence risk, but a longer treatment is likely not efficient.(39)

2.2.2 Epilepsy

In contrast to an epileptic seizure, epilepsy is defined as a brain condition in which the predisposition for generating epileptic seizures is persistent. There are various reasons for developing epilepsy and above all, at least one epileptic seizure is needed for diagnosing epilepsy. Additionally, further investigations (e.g. EEG,MRI) are mandatory to support the predisposition for further epileptic seizures.(34, 36) More than 50% of patients who experienced the first seizure tend to have a seizure recurrence.(41)
As already mentioned, epileptic seizures have multiple causes which can range from genetic predispositions, such as ion channel or transmitter receptor mutations, to several metabolic defects, congenital and perinatally earned brain damage or malformations. Moreover, inflammatory trauma implications, CNS tumors, vascular lesions, tuberous sclerosis etc. are also causes for developing epileptic seizures. So far, epilepsies have been grouped in symptomatic, idiopathic and cryptogenic epilepsies in order to disburden the complexity. The new classification model by Berg et al., 2008(41), proposed another etiological designation of epilepsies, namely from `symptomatic´ to `structural/metabolic´, `genetic´ instead of `idiopathic´ and replace `cryptogenic´ with `unexplained´.
The commission of the ILAE compiled broader proposals of classification, which have been adapted to the formerly mentioned suggestions from Berg et al., 2008(41). The aim of

classification is relevant when it comes to clinical practice, as it allows an accurate diagnosis which guides a suited treatment.(42)
According to the ILAE definition from 2014, which is still current, epilepsy may be diagnosed after a single unprovoked seizure if there is a significant risk of further unprovoked seizures.(38)
This is applicable to the following constellations:

1.) At least two unprovoked seizures which are more than 24 hours apart.
2.) One unprovoked seizure and a high risk for other seizures, which correspond to a general risk of recurrence after two experienced unprovoked seizures (at least 60%) within the next ten years.
3.) The diagnosis of an epilepsy syndrome.

It also must be mentioned that epilepsy does not obligatory require an unprovoked seizure. The presence of permanent change with a higher predisposition of generating further seizures is needed.(39)

2.3 Levetiracetam

Levetiracetam, by IUPAC classification named (2S)-2-(2-oxopyrrolidin-1-yl)butanamide, is an antiepileptic substance belonging to the pyrrolidine class and is a widely used substance for seizure prevention. In the late 1990 it was first approved by the Food and Drug Administration (FDA) for the clinical use for adjunctive treatment of parietal onset seizures in adults.(6) In August 2023 Levetiracetam was even included on the Model List of Essential Medicines (EML) by the World Health Organization (WHO) for partial-, generalized onset seizures and status epilepticus.(43)

This list contains several substances that are considered as the most effective, safe and important drugs in a health care system and is updated every two years since 1977. (43, 44)

After approvement by the FDA it became one of the first-line antiepileptic agents within ten years.(6, 46)

Discovery of Levetiracetam is related to the racetam family of drugs, to which Piracetam also belongs. Last was developed as a nootropic drug, with aim of improving cognitive function. Thus, structural modifications of piracetam led to the synthesis of levetiracetam, which exhibit anticonvulsant properties with reduced adverse effects such as sedation or cognitive impairment.(7)

Although Levetiracetam is a commonly used antiepileptic drug, its exact mechanism of action is not fully understood.

Its mechanism of action is postulated to be unique among other known and used antiepileptic substances. The key driver of levetiracetam's effectiveness is suggested to be the binding to the synaptic vesicle protein 2A (SV2A). SV2A is a membrane linked protein, widely found and important for the transmitter release.(6) By binding to SV2A, Levetiracetam modulates neurotransmitter release by stabilizing neuronal activity without a direct impact on ion channels or GABA/glutamate receptors, contrary to other antiepileptic drugs. Therefore, it has a broad spectrum of anticonvulsant activity and less side effects, compared to other anticonvulsant drugs.(6)

Regarding pharmacokinetics, referring to the impact the body has on the substance, levetiracetam has a high oral bioavailability over 95% and is not affected by intake of food. Peak plasma concentration is achieved within one hour and the elimination half-life lasts approximately six to eight hours. Levetiracetam is available as intravenous and oral formulation. Orally it is usually administered twice a day. Dosage for adults starts initially with 250 mg twice a day, following a dosage titration up to 500 mg twice a day after two weeks. The maximal dosage is defined as 1500 mg twice a day and can be achieved by dosage increase, with dose changes made in 250 mg or 500 mg steps.(7) Additionally, the

substance is not metabolized by the liver. However, in patients with impaired renal function the dosage has to be adapted as the substance is primarily eliminated by the kidneys. Levetiracetam is not significantly metabolized by the liver and its cytochrome P450 enzymes, but it also has a low protein binding, less than 10%. Therefore, a low potential for drug-drug interactions makes levetiracetam a favorable substance and it is beneficial when talking about polytherapy, especially in elderly patients with complex medication regimens. Although levetiracetam is generally well tolerated, it brings up a range of adverse effects such as somnolence, dizziness, fatigue, irritability, headache etc. Additionally, there are also some unwanted neuropsychiatric effects, more prevalent than in other antiepileptic drugs, like agitation, anxiety, depression, behavioral disturbances or even rare cases of psychosis or suicidal ideation.(6, 7) Vigilance for neuropsychiatric side effects is important as the behavioral and mood-related side effects are observed especially in long-term use and need to be evaluated mainly in vulnerable populations.

2.4 Guideline Recommendations for Antiseizure Medication (ASM) Use Relevant for Neurosurgical Perioperative Setting

A simple online search within several societies and guidelines shows the following information about ASM use which is presented in the Table below. Unfortunately, there is a lack of specific information on general ASM use in the perioperative neurosurgical setting. Therefore, relevant information was obtained from more specific indications. In the following Table, guideline recommendations are differentiated with respect to primary prophylaxis (PP) and secondary prophylaxis (SP).

Society/Guideline	ASM as PP	ASM as SP	Comments
Austrian Society for Neurosurgery (ÖGNC; *Österreichische Gesellschaft für Neurochirugie*)	No information	No information	No comment
Austrian Society for Neurology (ÖGN; *Österreichische Gesellschaft für Neurologie*)	No information	No information	Consider informations from German Society of Neurology (DGN)
German Society of Neurology (DGN, *Deutsche Gesellschaft für Neurologie*) S2k guideline recommendation from the DGN, published in September 2023(36)	No information	If symptomatic seizure no ASM indicated, if ASM was still considered then ASM discontinuation after acute phase after 7 days or at patients admission	No comment
German Society for Neurosurgery DGNC, *Deutsche Gesellschaft für Neurochirurgie*)	No information	No information	No comment
European Academy of Neurology (EAN)	No information	No information	No comment
European Association of Neurosurgical Societies (EANS)	No information	No information	No comment
European association of neuro-oncology (EANO) and the European Society for Medical Oncology (ESMO)(5)	No ASM as PP recommendation	ASM should be placed, at least transiently	No comment
International League against epilepsy (ILAE)	No information	No information	acute symptomatic seizure definition cope with DGN(36); no further ASM on-set info found

Table 1 Overview of Guidelines referring to ASM use in individual indications

Society/Guideline	ASM as PP	ASM as SP	Comments
World federation of neurosurgical societies (WFNS)	No information	No information	No comment
American Academy of Neurology (AAN)	No information	No information	No comment
American epilepsy society (AES)	No information	No information	No comment
American Heart Association and American Stroke Association (AHA/ASA)(47)	No recommendation of PP in patients with spontaneous intracerebral hemorrhage (sICH)(47)	No information	No comment
Brain Trauma foundation "guidelines for the Management of severe TBI, 4th edition" completed 2016(48)	insufficient evidence supporting a Level I recommendation. for ASM as PP.(48)	No information	Phenytoin as PP (< 7 days) if overall benefit is outweighing accompanied complications, (Level II A recommendation) preventing early but not late post traumatic seizures.(48)
American College of Surgeons (ACS) "The management of TBI"(49)	use of ASM prophylaxis for 7 days following TBI is considered to avoid ePTS. A continuation of ASM prophylaxis > 7 days in patients without clinical EEG seizure activity or with seizure activity solely within the first 24 hours post injury, is not recommended.(49)	No information	No comment

Table 2 Overview of Guidelines referring to ASM use in individual indications

Nevertheless, **DGN(36) and EANO and ESMO(5)** are highlighted, as their recommendations are more precise and will be mentioned in a further chapter with the synthesized recommendations for the perioperative neurosurgical setting.

Although the DGN does not mention any specific related information with exact link to the neurosurgical perioperative period in patients without a diagnosed epilepsy, a clear statement in terms of the first seizure in adults is given. The DGN points out that after an acute symptomatic seizure, independent of origin (structural or systemic linked), long-term seizure suppressant is not recommended and should therefore not be administered. (Consenus strength: 92.2%) If an antiseizure medication (ASM) is administered due to individual consideration of the prescriber after an acute symptomatic seizure, the DGN suggests discontinuing the ASM after the acute phase. This is usually defined as the timepoint of discharge or transfer of the patient. This is linked to the low long-term risk of seizure recurrence of a new, then unprovoked, seizure. (Consensus strength: 94.1%)(36, 40)

Definition of acute-symptomatic seizure with different etiology, modified from DGN S2k-Guideline *„erster Epileptischer Anfall und Epilepsien im Erwachsenenalter"*(36) published by Beghi et al., 2010.(37)

Etiology	**Time window**
Systemic disorders and diseases	
Metabolic disorders For example, glucose < 36 mg/dL, sodium < 115 mmol/l	Within 24 hours of commencement
Alcohol abstinence	Within 7-48 hours after abstinence
Substance intoxication (e.g. cocaine)	Within duration of substance activity
Acute brain damage	
Cerebrovascular events, craniocerebral trauma, CNS surgery, global hypoxia	Within 7 days
CNS infection, autoimmune encephalitis	During acute phase

Table 3 adapted and translated from DGN guidelines "Erster epileptischer Anfall und Epilepsien im Erwachsenen Alter" and Beghi et al., 2010.

The **European association of neuro-oncology (EANO) and the European Society for Medical Oncology (ESMO)(5)** state in their guidelines "Neuro-Oncology and vascular complications of primary and secondary brain tumors: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow up" that no ASM is recommended for primary prophylaxis in brain tumor patients. For brain tumor patients who

have experienced a seizure, an ASM treatment as secondary prophylaxis should be prescribed, at least transiently. Furthermore, therapeutic intervention against brain tumors also contribute to seizure control, not only including surgery but also radio therapy or chemo therapy.(5)

3 Aim of Thesis

The first part of this thesis is a systematic literature review, summarizing evidence-based recommendations alongside guideline recommendations regarding the pharmacological use of newly prescribed levetiracetam in patients in a neurosurgical setting.

The aim is to synthesize evidence-based criteria for prescribing levetiracetam in the perioperative neurosurgical setting including indication, dosing and therapy duration. Two indications for levetiracetam in the perioperative neurosurgical settings are considered, i.e. prescribing it as primary prophylaxis (prophylactic use without prior seizure) or as secondary prophylaxis (therapeutic use after seizure occurrence).

The second part of the thesis comprises the results of a medication use evaluation (MUE) of levetiracetam in neurosurgical patients. These results will be compared with the previously established evidence-based prescribing criteria for levetiracetam in this patient population.

Obtained insights from the systematic literature and the medication use evaluation are intended to contribute to optimizing the use of levetiracetam prescriptions, thereby helping to avoid unjustified or prolonged prescriptions.

4 Methodology

4.1 Systematic Review

4.1.1 Databases and Search Strategy

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)(50). Ethics committee approval was granted by Version 03 on the 30th of April, 2025 and is attached in the Appendix 10.5. No specific predefined protocol for the literature review was registered. A Literature search was conducted in October 2025 in two databases, PubMed (MEDLINE) and EMBASE, to improve coverage and avoid missing of relevant studies and information. These two databases were chosen based on their comprehensive indexing of biomedical and clinical literature in relevant alignment for the topics, ensuring breadth but also depth on the subject matter. To obtain data, the search was limited to published studies between January 2015 and September 2025. To observe and ensure a structured and reproducible approach, a systematic search strategy over both databases was performed.

4.1.2 Strategies and Search Terms:

In accordance with the PICO framework, several synonyms and controlled vocabulary terms were identified to outline the predefined research questions. Both free-text terms and controlled vocabulary (e.g. MeSH in PubMed, Emtree in EMBASE) were used. Various combinations of the following key terms were applied to ensure high sensitivity. The following Table presents the used keywords according to the PICO framework predefined research question.

PICO Element	Definition	Example Keywords/Synonyms
P- Population	Patients in neurosurgical setting	Neurosurgical procedures, brain surgery
I- Intervention	Administration of LEV	Levetiracetam (LEV)
C- Comparison	Any comparator, as well no therapy	-
O- Outcome	Seizure prophylaxis in patients with and without experienced seizure	seizure
T- Timeframe	Perioperative period (pre-intra- and postoperative)	Peri-, pre-, intra-, postoperative

Table 4 PICO elements table with the respective definitions

To combine search terms representing seizure prophylaxis, Levetiracetam and neurosurgery, Boolean operators (AND/OR) were utilized.
To ensure full transparency and reproducibility, detailed information containing the complete search strings is attached in the Appendix 10.1.

4.1.3 Inclusion and Exclusion Criteria

The eligibility criteria were defined in accordance with the PICO framework. Filters were applied to the combined final search term strings.
The following filters were chosen to enhance the quality of included papers: Meta-Analysis, Network Meta-Analysis, Reviews, Systematic Reviews. Works published in English and German were included and only human related topics were considered. Preclinical research works and animal studies were excluded as they did not meet the inclusion criteria for this work. Additionally, only papers investigating a human population aged over 18 years were included and papers concerning only pediatric issues were excluded. Furthermore, papers which solely compared levetiracetam with other ASM considering efficacy in seizure prevention were also excluded from the systematic review, as comparison of antiepileptic substances was not included in the frame of this work. Papers addressing topics such as toxic seizures, treatment of epilepsy and nonconvulsive/convulsive status epilepticus were also not taken in consideration and disregarded due to lack of relevance for the main research question concerning this work.

4.1.4 Screening, Data Selection, Extraction Process and Synthesis

The study selection process was aligned with the PRISMA guidelines.(50) All respective articles, which aligned with the inclusion criteria, were exported to EndNote21®, a program in which all the direct sources from the literature database can be integrated and sorted. Additionally, sustained by the program, all duplicates were taken in consideration from both databases and the respective duplicates were eliminated. Retrieved records were screened by one person, the author of this thesis. First, title and abstract screening was performed to identify potentially relevant reviews. Second, full text screening of the chosen literature was done to sustain the eligibility based on the predefined criteria.
All relevant articles which were appropriate regarding the research questions and in alignment with the inclusion criteria, were considered for the final analysis. For all included works a standardized form, which was developed by the author of this work, was used to extract important data from the included literature, listing for example title, author, year etc., and is mentioned in the Appendix 10.2.
To minimize the bias and enhance transparency and reproducibility, the screening process followed a structured approach, which is also visualized in the attached PRISMA flow

diagram. A total of 10 works were included in the qualitative synthesis as they met the inclusion criteria. Due to the heterogeneity of the analyzed publications, an early categorization for each indication was performed as results were not suitable for generalization. Therefore, neurosurgical key categories were chosen, and respective works found within the literature search were assigned. More details are found in the results chapter.

4.1.5 Quality Assessment

A validated tool, Measurement Tool to Assess Systematic Reviews (AMSTAR-2)(51), was utilized to appraise the quality of the included works. This validated tool by Shea et al., 2017 (51), enables the critical evaluation of the quality of systematic reviews. It consists of 16 items assessing relevant key factors which contribute to the overall quality of a systematic review.

For each included work, the entire official protocol questionnaire was performed. All results generated from the online checklist were used to produce the automated final result, which is summarized in the concise overview, displayed in the Appendix 10.4.

AMSTAR-2 grading possibilities are high, moderate, low and critically low quality. Moreover, AMSTAR-2 accounts critical domains which are presented in the Appendix 10.4. The overall result depends on the number of critical items met.

4.2 Medication Use Evaluation

Before initiating the systematic literature review and the retrospective data collection, a detailed project plan was designed, corresponding to the requirements of the Ethics Commission of the Medical University of Vienna. This was, amongst others, mandatory in accordance with Good Scientific practice as patient data was processed within the retrospective data analysis. The project plan was accepted as Version 03 on the 30th of April, 2025, and is attached in the Appendix 10.6, to provide full transparency. Following contents are included in the attached project plan:

- Aim of the Study
- Study Design
- Eligibility Criteria and Elected Parameters
- Patients and Data Acquisition
- Methodology
- Data Analysis
- Data Protection

4.2.1 Study Design

A retrospective descriptive data collection was performed over a period of six months, including May till October 2024. All involved patients were over 18 years of age and treated at the Department of Neurosurgery at the Vienna General Hospital in the mentioned period. Additionally, all included patients followed a surgical intervention at the named department and had an inpatient stay at the hospital in this time. In the following, the study population is described considering inclusion and exclusion criteria.

4.2.2 Inclusion Criteria

- Patients aged ≥18 years
- Inpatient admission and surgical treatment at the Department of Neurosurgery, Vienna General Hospital
- New prescription of Levetiracetam during the inpatient stay, regardless of dosage or administration method

4.2.3 Exclusion Criteria

- Patients with a diagnosis of epilepsy at the time of admission
- Patients diagnosed with epilepsy during the inpatient stay
- Patients who were already on a long-term Levetiracetam regimen prior to the inpatient admission

4.2.4 Data Extraction, Analysis and Protection

For all patients meeting the inclusion criteria, the MUE was performed using the hospital information system AKIM. To narrow the search results, the respective timeframe was chosen, and the search was filtered to include only the neurosurgical department by referencing its cost unit identification number. Relevant data, including patient and case numbers, were extracted using SAP Business Warehouse (BW)®. Adult neurosurgical units at the Vienna General Hospital consist of one intensive care unit (ICU) and two standard care wards. After obtaining the results, all data were compiled into an Excel® sheet. A first round of data extraction was performed, eliminating duplicate patients and case numbers, as well as patients who did not meet the inclusion criteria.

The analysis of demographic and clinical data to describe the patients population was performed by using descriptive statistical measures such as mean standard deviation.

The primary endpoint `Degree of concordance of Levetiracetam prescription in the context of seizure prophylaxis without experienced seizure´ was calculated as the percentage of prescription in alignment with evidence-based criteria out of all LEV prescription for seizure prophylaxis during the data collection period. The percentage is shown both as an overall value and separately for the domains of dosage and duration.
The secondary endpoint `Degree of concordance of Levetiracetam prescriptions in the context of seizure prophylaxis after experienced seizure´ was calculated as the percentage of prescriptions that align with evidence-based criteria out of all LEV prescription for seizure therapy during the data collection period. The percentage was shown both as an overall value, as well as separately for the domains of dosage and duration.
Data analysis was performed with IBM SPSS® Statistics Version 29.0.

As the project required the collection of personal data from all the included patients in this study, data was collected within the scope of this project. This referred to e.g. medical findings, patient histories, treatment methods, medication from long-term prescriptions, newly prescribed drugs in the perioperative setting and other personal information contributing to optimal documentation and data collection. Access to the medical data was feasible within the scope of the authors professional role as a clinical pharmacist, providing clinical pharmaceutical care at the neurosurgical ward. Those findings were handled in a pseudonymized form and there was not any direct reference to the patient’s name. Documentation was performed by an assigned case number (numeric) and concomitant running number in Excel® spreadsheet. Further information is found in the attached project plan Appendix 10.5 and 10.6.

5 Results

5.1 Systematic Review

5.1.1 Data Extraction and Synthesis

A total number of 3241 articles were identified with the previous presented search terms. 91 articles, deriving from both databases, were exported into EndNote21® after setting filter. In general, 91 papers were screened for title and abstract. According to the inclusion criteria 28 papers were fully screened and compared also by the total conclusions retrieving from the paper. One work from Gigliotti et al., 2021(52), was identified as a duplicate, within the search in both databases, and eliminated. As not all of the 28 papers corresponded with the research questions, 13 papers were excluded. After a second round of reading, 5 papers were again excluded because of limited coverage of content with the research questions. A total number of 10 studies fulfilled the inclusion criteria and were included in qualitative synthesis. Due to the width of the topic an early categorization for each indication was considered in order not to mix up the information and to stick to the systematic methodology. Following neurosurgical key categories were chosen and respective works found within the literature search were assigned:

- Traumatic brain injury (TBI) → 3 papers
- Subdural hematoma (SDH) → 1 paper
- Spontaneous intracerebral hemorrhage (sICH) → 1 paper
- Brain tumors (BT) → 3 papers
- Mixed, considering above mentioned subgroups, Neurocritical care (NC) → 2 papers

PRISMA Flow Diagram:

To illustrate the whole selection process a PRISMA flow diagram is implemented below including the exact number of all screened articles. Additionally, all excluded articles, depending on which stage the exclusion was performed, are also visible to enable full transparency and traceability.

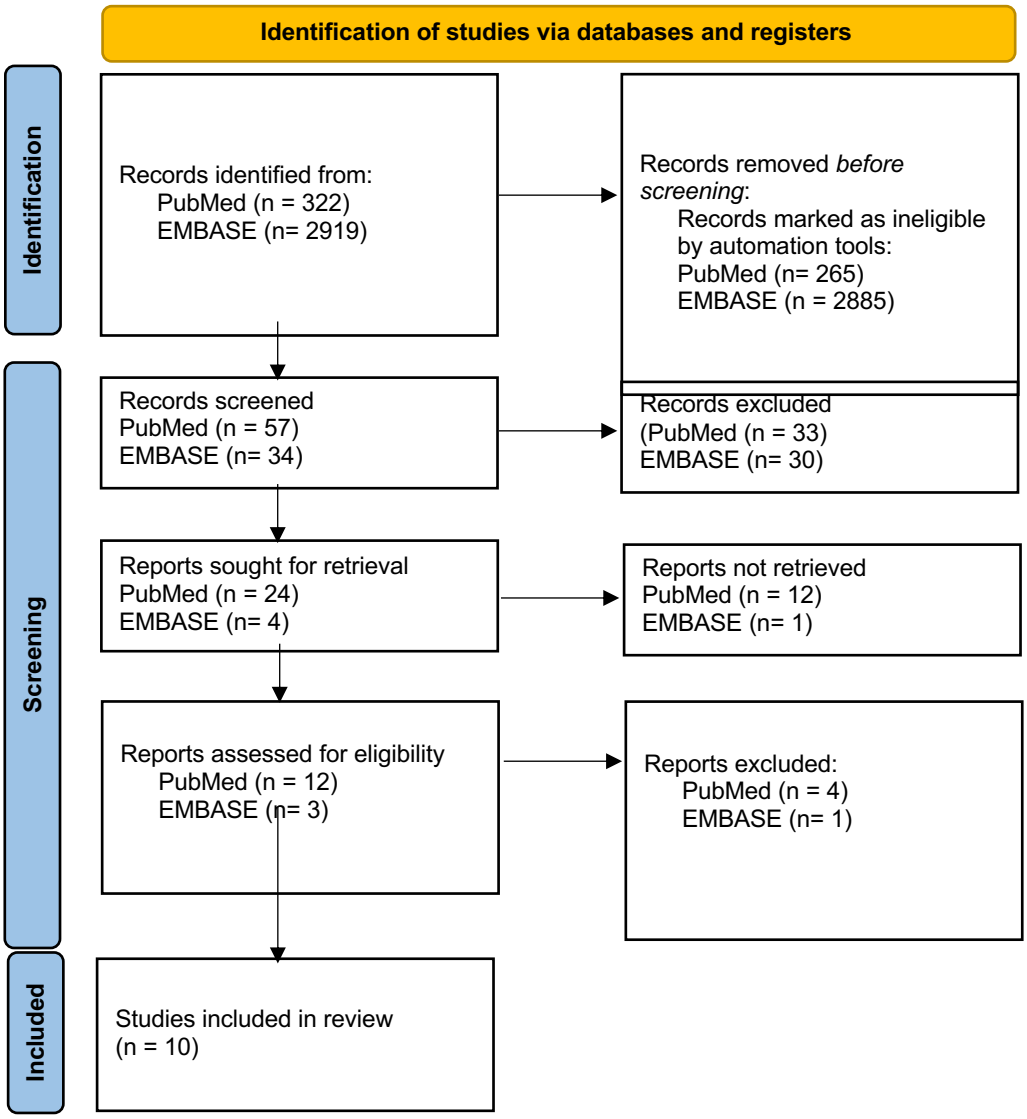

Figure 1 Prisma flow diagram

5.1.2 Included Studies Summary

The following section provides a concise overview of findings from the included studies which were published between 2015 and 2025. Most of them focused on the prophylactic administration of levetiracetam in the perioperative neurosurgical setting. All of the 10 included publications were systematic reviews. Quality appraisal for each included work is also reported. The quality assessment was performed with the validated quality assessment tool AMSTAR-2.(51) A subgroup-based approach was taken into consideration due to the presence of methodological heterogeneity among the included studies. Findings were organized according to the already presented key categories. This subgroup-based analysis approach enabled a more detailed synthesis of evidence regarding the perioperative use of levetiracetam in different patient populations. Due to substantial heterogeneity among the included studies, study population and variability in outcome definitions, a narrative synthesis was chosen. After the following narrative summary of the results by subgroup, a summary overview of all included studies is presented.
Additionally, an extended and more detailed summary of each included study is provided in the Appendix 10.2.

Traumatic Brain Injury (TBI):

Three systematic reviews and meta-analyses addressed the efficacy of prophylactic use of LEV in patients with TBI in preventing occurrence of posttraumatic seizure.(2, 53, 54) All three reviews considered observations over similar time periods. Frontera et al., 2024(2) investigated short vs long ASM therapy duration. In contrast Wilson et al., 2018(53) investigated seizure incidence of early post traumatic seizure (ePTS), defined as a period of
< 7 days after TBI, and late post traumatic seizure (lPTS), referring to seizures occurring > 7 days after TBI.
All authors referred to the same cut off time point of 7 days for posttraumatic seizure occurrence and ASM prophylaxis.
A total amount of 58 studies were included in all 3 reviews in this subgroup. In the work of Frontera et al., 2024(2), the largest sum of works was included, counting 33 publications.
Regarding inclusion criteria all three systematic reviews demonstrated similar patterns such as TBI, hospitalized adults over 18 years of age and without seizure history. However, it must be mentioned that the work of Wilson et al., 2018(53), also addressed the findings of an included pediatric population with a tendency to lower incidence of PTS than adults. This applied to both included studies comparing LEV vs. placebo from Wilson et al., 2018.(53) The publication pointed out that this may have increased the sample size required to detect a difference in lPTS.

Severity of TBI was categorized and highlighted in every work. All considered inclusion of mild to severe TBI and sub categorized on trauma severity. Moreover, efficacy of seizure prevention was not investigated solely on LEV but also on other ASM.

Wat et. al., 2018,(54) included 9 publications in their systematic review, from which just one study investigated the use of LEV. The other included studies considered other ASM. Therefore, no subgroup analysis could be performed in that review. In addition, regarding the one included study with LEV, no dosage was reported. Overall, it must be noted that all three reviews do not provide any specific information on dosage as included studies are heterogeneous.

Therefore, the reviews do not support any specific recommendation regarding ASM dosage for seizure prevention.

Investigation on efficacy of LEV as prophylaxis was either compared to other ASM or to no treatment or placebo among the included publications. Regarding ePTS, within < 7 days after TBI, comparable efficacy for PHT and LEV has been described. Wat et al., 2019(54) reported that more literature and evidence are available for PHT regarding seizure prevention, as it is an older substance. In contrast, fewer data are available for LEV, since the substance is newer and has been less extensively studied in this field.

Hence, Wilson et al., 2018(53) and Frontera et al., 2024(2) do no support one substance over the other regarding seizure prevention efficacy, as they seem comparable. On the other hand, LEV has a more favorable pharmacologic aspect with less adverse events. This finding is sustained and outlined in the reviews.

Wat et al., 2019(54), described a modest benefit in observational studies of ASM in general for ePTS, but convincing evidence regarding ASM effectiveness as prophylaxis for ePTS is missing. In contrast to this finding, Frontera et al., 2024(2), reported no statistic significant difference considering early and late seizure events comparing ASM use vs. no ASM use.

Nevertheless, if ASM use is considered, then a short duration < 7 days is recommended.

All three systematic reviews sustain that no clear advantage of a long prophylaxis could be demonstrated for primary prophylaxis with LEV beyond a period of 7days after TBI.

Limitations were reported by the authors of the reviews as comparison between the included studies showed difficulties since study populations and treatment duration were heterogeneous and follow ups were partly missing. Furthermore, the majority of the studies were retrospective and underpowered, highlighting the need for more prospective studies with lager study population.

Subdural Hematoma (SDH):

For this subgroup a systematic review by Won et al., 2017(55), was included. This work considered 24 studies and investigated the incidence and risk of ePTS and lPTS in patients

with acute SDH (aSDH) and chronic SDH (cSDH), as well as the evidence of ASM use in SDH. The overall incidence of ePTS and lPTS is generally higher in patients with aSDH than in those with cSDH. Definitions for several seizure risk situations were provided in aSDH, such as preoperative and 24h post operative, low Glasgow-coma-Scale (GCS-Scale) and craniotomy. Since a higher PTS incidence in aSDH was demonstrated, estimated with about 28% PTS risk, the prophylactic ASM use in severe aSDH may be considered but with a treatment limitation to 1 week. In contrast, patients with cSDH demonstrated an estimated PTS incidence of 10% and ASM treatment must be evaluated individually based on cumulative risk factors. Those may be alcohol abuse, change of mental status, previous stroke and hematoma density on the computed tomography (CT). Nevertheless, the review did not provide exact information on the number of included studies investigating LEV, nor on the number of patients investigated. Only general statements were addressed regarding primary seizure prophylaxis and the similar efficacy of PHT compared to LEV.

Due to the heterogenous report of early and late PTS definition among included studies and lack of ASM therapy onset timepoints, dosage and duration, Won et al., 2017(55) assessed these limitations as risk of bias and did not address any specific recommendations. However, Won et al., 2017(55), emphasized the need for controlled prospective studies, as the majority of studies included in the review were retrospective.

Spontaneous Intracerebral Hemorrhage (sICH):

One review from Gigliotti et al., 2021(52), was included in this subgroup, comprising 7 studies published between 2012 and 2020. This review focused on seizure prevention, functional outcome, and mortality in patients with sICH receiving LEV vs. no ASM. Only studies with class lll evidence were included, in which six studies were cohort studies and one was a case control study. In a pooled analysis, Gigliotti et al., 2021(52) did not reveal any significant effect on prevention of seizure occurrence in the LEV treatment group. Controversially, the use of prophylactic LEV was even associated with a poor functional outcome on the modified rankin scale (mRS) > 3. A clinical outcome measurement scale that evaluates disabilitiy and dependence in daily activities, with higher scores indicating a greater impairment. A non-significant trend toward reduced mortality was observed in LEV group. Follow-up was generally 90 days, although two studies did not report follow-up time. Several limitations were reported such as inclusion of retrospective studies, confounding factors inherent to retrospective data, differences in sample size between LEV and no ASM groups, and variability in outcomes. Overall, the quality of evidence was rated as low according to GRADE criteria, and results should be interpreted with caution. Moreover, poor

quality of the current available data highlights the need for better randomized clinical studies investigating prophylaxis with LEV in this subgroup.

Brain Tumor (BT):

Three studies were identified that investigated the perioperative use of LEV as seizure prophylaxis in patients with brain tumors which underwent neurosurgical procedure.

Two systematic reviews with meta-analysis from Pourzitaki et al., 2016(56) and Batista et al., 2023 (57), were taken in consideration. The third included work, from Walbert et al., 2021(58), was a systematic review and practice guideline update.

Pourzitaki et al., 2016(56) included 12 observational studies in their systematic review, both pro- and retrospective. Their work focused mainly on the LEV administration in the perioperative course as prophylaxis and investigated efficacy, measured as seizure occurrence, and safety. These findings were compared to other ASM or no therapy. Patients with brain tumors undergoing biopsy or craniotomy were included. LEV treatment was commenced preoperatively. Outcome assessment was observed on different time points, as early postoperative period was defined within 48h after intervention, late postoperative period was defined as 48h till 4 weeks postoperatively and late observation period was defined beginning 4 weeks after surgery. Eight out of twelve included studies assessed outcomes between 48h hours and 4 weeks post intervention. Overall, study durations ranged from 7 days to 12 months, and the route of drug administration (intravenous or oral) was documented. Different dosages ranging from 500-3000 mg LEV per day, were considered. Owing to the small number of included trials, data extraction referring to seizure incidence was not possible through different study periods. Additionally, a risk of bias was documented due to lack of randomization technique and data of blinding. Nevertheless, this study suggested that routine perioperative LEV may be more effective than PHT in reducing postoperative seizure occurrence after neurosurgical interventions, however, no exact recommendation was provided.

In contrast Batista et al., 2023(57), investigated whether ASM use provides advantage over no ASM with respect to seizure occurrence in the perioperative neurosurgical setting in patients with brain tumors. This systematic review included 9 studies, with 4 of them investigating on LEV use considering patients with meningioma. Observation time within the early postoperative period was 7 days and from 7 days up to 12 months in the post intervention period. The main findings indicate that prophylactic ASM use is not universally justified, as seizure frequency was not significantly reduced. Nevertheless, high heterogeneity among included studies was again reported and no sufficient evidence was documented regarding the prophylactic use of ASM post neurosurgical intervention in

patients with meningioma. Therefore, no clear conclusion could be drawn for this population.

The last systematic review and practice guideline update from Walbert et al, 2021(58), consisted of 37 studies focusing on the seizure free survival and first seizure frequency within 6 months from diagnosis of brain tumor in patients without documented seizure with ASM compared to no ASM. Further, another aim was to demonstrate if there was any difference considering perioperative ASM vs. no ASM prophylaxis in seizure occurrence and if there was any impact on seizure occurrence within 14 days post neurosurgical intervention. As different research questions were addressed, heterogeneity among the included works was observed considering timing of intervention and duration of prophylactic treatment. It must be mentioned that no specific information about dosage was given. In conclusion, Walbert et al., 2021(58) highlighted that ASM was not effective regarding primary seizure prophylaxis in seizure naïve patients with newly diagnosed brain tumors. Moreover, ASM prophylaxis also did not seem to increase the seizure free survival or reduce seizure frequency at 6 months from diagnosis. Also, ASM prophylaxis was possibly not effective in overall seizure reduction. Overall, Walbert et al., 2021(58) points out, that ASM prophylaxis seemed not to be effective in seizure reduction following 14 days after intervention. Seizures seemed to be more common in patients with low-grade glioma (58). Data was insufficient for sustaining the need of prophylactic ASM in these patients. Furthermore, there was also lack of literature addressing newer surgical approaches which are associated with a higher seizure risk, such as motor mapping or awake craniotomies. Although significant progress has been made in defining patient subgroups by combining molecular markers with histopathology, it remains unclear how to connect this information into seizure risk stratification in brain tumor patients. Crucial clinical questions of the impact of molecular markers on seizure development still need to be addressed in further studies. Due to methodological limitations within the published evidence, it was not possible to identify higher risk populations or pinpoint subpopulations. Nevertheless, based on this work, the following recommendations were made. There was no effect on overall seizure reduction visible, therefore no ASM prescription in these groups of patients as primary prophylaxis can be recommended. Additionally, there is insufficient evidence for ASM recommendation as seizure risk reduction in the peri- and postoperative period overall and also 14 days beyond surgical intervention. Nevertheless, physicians may choose LEV than other ASM due to lower side effects and LEV being comparable to previous first generation ASM when investigating prevention of early postoperative seizure prevention within 7 days of surgery.

Mixed, Considering All Subgroups:

Within the literature search, 2 systematic reviews were found investigating several neurosurgical patient subgroups. The first included work from Fang et al., 2022(59), considered patients over 18 years of age with TBI, ICH, SAH and supratentorial neurosurgical intervention and compared LEV vs. other ASM or vs. no ASM prophylaxis. This systematic review included 30 studies. A dosage of LEV 500 mg twice a day was mostly used (11 of 23 studies, LEV in all dosages was used in 23 of 30), but in general dosages ranged in between 250-1500 mg twice daily. Fang et. al., 2022(59), points out that the used LEV dosages between 250-500 mg twice daily may have been subtherapeutic. These dosages were used in 11 out of 30 studies. No statistic significant seizure reduction could be demonstrated when comparing LEV vs. other ASM and vs. no ASM.

Fang et al., 2022(59), also mentioned that there was no clear evidence of a significant reduction of first seizure incidence in TBI, SAH or ICH patients. No benefit for the prophylactic LEV use vs. other ASM vs. no ASM could be detected in the pooled patient cohorts. In contrast, for patients who underwent supratentorial neurosurgery, LEV may be favored over other ASM due to fewer reported side effects. Additionally, the supratentorial neurosurgery group seemed to benefit from prophylactic LEV. Nevertheless, it must be kept in mind that considering the supratentorial neurosurgery group, there may have been a risk of bias, as those patients ranged in diagnosis from brain tumors to intracerebral hemorrhage and these differences may have influenced the subsequent seizure risk. Due to heterogeneity and moderate to serious risk of bias among all included studies, the authors of this work neither support nor strongly recommend against the prophylactic LEV use in these patients (TBI; SAH, ICH and supratentorial neurosurgery). Especially duration of prophylaxis with ASM was generally not clearly documented in this work. SAH guidelines were cited suggesting ASM prophylaxis other than PHT, for 3-7 days but also highlighting the weak recommendation based on low quality evidence.

The work from Jiang et al., 2025(60), included 27 works: 20 evidence-based guidelines, 6 expert consensus and one non-evidence-based guideline. All included publications were issueded from international organizations and addressed multiple neurosurgical subgroups. European guidelines were cited most commonly with a focus on TBI. Additionally, it must be mentioned that one guideline was also addressing a pediatric population. Jiang et al., 2025(60), investigated the methodological quality of the guideline recommendations with the aim of summarizing all aspects of the recommendations. This was performed for primary prophylaxis, without seizure events, as well as for secondary seizure prevention in the neurosurgical field. Jiang et al., 2025, highlights the classification of seizures with immediate seizures (occurring within 24h of injury), early (within 7 days of injury) and late seizures (more than seven days after injury).(61) The incidence of PTS without prophylactic ASM

use is estimated to be between 4-25% regarding ePTS and 9-45% in lPTS. Referring to guideline recommendations, in patients without documented seizures in the neurosurgical setting, the prophylactic use of any ASM was not recommended, regardless of diagnosis.

For specific clinical conditions, such as TBI or cerebral venous thrombosis/cerebral venous sinus thrombosis (CVT/CVST) variations regarding seizure risk may exist. For tumors, there are difficulties to establish a strict temporal boundary to identify seizures as acute symptomatic, based on the slow growing nature of tumors. Therefore, ideal therapy initiation and discontinuation remain unclear and no exact recommendations for therapy duration can be made. Accordingly, in patients without experienced perioperative seizures, a discontinuation of ASM is recommended, if a primary prophylaxis was started initially. Discontinuation times range from 3 to 7 days, one week or even two-weeks post-surgery.

Considering patients with supratentorial craniocerebral surgery and brain tumors who experienced a first seizure, medication initiation is recommended by several guidelines as soon as possible. Unfortunately, no specific information about duration and dosages are addressed to this topic. Additionally, ASM duration varies from three days to two years after seizure occurrence, depending on whether seizures occurred preoperatively or postoperatively.

Jiang et al., 2025(60), mention that after postoperative seizure occurrence, ASM duration can be extended to three months, and up to one year and may be continued at least for one to two years in patients with a history of preoperative seizure. It is worth mentioning, that they refer to three studies: two on gliomas and one Chinese guideline addressing supratentorial craniocerebral surgery from 2022.(62-64) In patients with glioblastoma and anaplastic glioma, with postoperative refractory seizures or incomplete tumor resection, ASM discontinuation is not recommended.

Jiang et al., 2025(60), highlight the limitations of their available guidelines as there is a lack of detailed guidance regarding prophylactic initiation, dosage, and duration. To sum up, the authors of this work recommended 9 out of 27 included guidelines, eight with modifications and ten were not recommended.

Both works, investigated multiple neurosurgical subgroups and emphasized again the need of better randomized trials focusing on LEV for seizure prophylaxis in neurocritical care as the available studies are highly heterogeneous and limited regarding methodology.

The following Table presents an overview of the included studies and is sorted by the neurosurgical key categories. Within each category, studies are ordered chronologically by ascending year of publication, starting with the earliest.

Number	Indication	Reference: Author; Year	Publication type (SR/MA)	Incl. studies (n= x)	Main focus	P/T	Key findings	Quality assessment (AMSTAR-2)
1	TBI	*Wilson et al. 2018(53)*	SR/MA	16	Efficacy of LEV vs. Phenytoin (PHT) vs. no ASM for prophylaxis in early post traumatic seizures (ePTS) and late post traumatic seizures (lPTS) after TBI	P	Comparable efficacy of LEV and PHT in ePTS, no significant difference between LEV/PHT/no ASM	AMSTAR-2 Critically low
2	TBI	*Wat et al. 2019(54)*	SR/MA	9	Benefit of any ASM prophylaxis in patients with TBI	P	No outperformance of any ASM substance regarding efficacy, PHT most studied drug, no effective difference in treatment LEV vs. PHT, modest benefit of ASM use in early PTS	AMSTAR-2 Critically low
3	TBI	*Frontera et al. 2024(2)*	SR/MA	33	ASM in moderate-severe TBI without seizure history regarding early and late seizure occurrence; LEV over PHT used, duration of prophylaxis short vs. long	P	No statistic significant difference considering early and late seizures, LEV over PHT preferred, if ASM used – short duration < 7 days considered	AMSTAR-2 Critically low

Table 5 Overview and summary of included papers from the systematic review; TBI= traumatic brain injury; SDH= subdural hematoma; ICH= intracerebral hemorrhage BT= brain tumor; NC= neurocritical care (including TBI, SDH, ICH, BT..) SR= systematic review; MA= meta-analysis P= prophylaxis; T= therapy; AMSTAR-2 (high/moderate/low/critical low); incl.=includ

Number	Indication	Reference: Author; Year	Publication type (SR/MA)	Incl. studies (n= x)	Main focus	P/T	Key findings	Quality assessment (AMSTAR-2)
4	SDH	*Won et al. 2017(55)*	SR	24	Incidence and risk factors of e/l PTS, evidence ASM use as prophylaxis in SDH	P	ePTS and lPTS higher in aSDH than cSDH, prophylactic ASM use for 1 week in aSDH can be considered, cSDH evaluation of ASM use based on cumulative risk factors	AMSTAR-2 Critically low
5	sICH	*Gigliotti et al. 2021(52)*	SR/MA	7	LEV vs. no ASM as prophylaxis in seizure prevention/functional outcome/ mortality	P	No association in seizure reduction between LEV vs. no ASM; worse functional outcome with LEV prophylaxis, no statistical significance in mortality outcome	AMSTAR-2 Critically low

Table 6 overview and summary of included papers from the systematic review; TBI= traumatic brain injury; SDH= subdural hematoma; ICH= intracerebral hemorrhage; BT= brain tumor; NC= neurocritical care (including TBI, SDH, sICH, BT..) SR= systematic review; MA= meta-analysis, P= prophylaxis; T= therapy, AMSTAR-2 (high/moderate/low/critical low); incl.=included

Number	Indication	Reference: Author; Year	Publication type (SR/MA)	Incl. studies (n= x)	Main focus	P/T	Key findings	Quality assessment (AMSTAR-2)
6	BT	*Pourzitaki et al. 2016(56)*	SR/MA	12	Efficacy and safety of LEV in comparison to other ASM as seizure prophylaxis	P	Fewer seizure occurrence and side effects among LEV use in contrast to other ASM	AMSTAR-2 Critically low
7	BT	*Walbert et al. 2021(58)*	SR	37	Seizure free survival /overall survival/ first seizure frequency/ seizure risk reduction in early postoperative setting in patients with newly diagnosed primary or metastatic brain tumors with ASM vs. no ASM for prophylactic use	P	No effectivity of ASM as primary seizure prophylaxis; no increase of seizure free survival and reduction of seizure frequency 6 months from diagnosis; ASM prophylaxis following 14 days after surgery possibly not effective in seizure occurrence, lack of high evidence for increase of progression-free or overall survival with ASM	AMSTAR-2 Critically low

Table 7 overview and summary of included papers from the systematic review; TBI= traumatic brain injury; SDH= subdural hematoma; ICH= intracerebral hemorrhage; BT= brain tumor; NC= neurocritical care (including TBI, SDH, sICH, BT..) SR= systematic review; MA= meta-analysis, P= prophylaxis; T= therapy; AMSTAR-2 (high/moderate/low/critical low); incl.=included

Number	Indication	Reference: Author; Year	Publication type (SR/MA)	Incl. studies (n= x)	Main focus	P/T	Key findings	Quality assessement (AMSTAR-2)
8	BT	*Batista et al. 2023(57)*	SR/MA	9	Advantage of prophylactic ASM use vs. no ASM post neurosurgical meningioma resection	P	No significant reduction in seizure occurrence observed in patients with ASM as prophylaxis	AMSTAR-2 Critically low
9	NC	*Fang et al. 2022(59)*	SR/MA	30	LEV vs. other ASM or no ASM for prophylactic seizure prevention after neurosurgical event or hospital admission	P	No benefit for LEV use in comparison to other ASM and no ASM, no significant difference concerning seizure occurrence	AMSTAR-2 Critically low
10	NC	*Jiang et al. 2025(60)*	SR	27	Methodological guideline/recom-mendation quality of primary and secondary seizure prevention	P/T	ASM as primary prevention: 3 days – 2 weeks Therapy following postoperative seizure: 3 months to 1 year preoperative seizure history: ASM continuation 1-2 years post-surgery	AMSTAR-2 Critically low

Table 8 overview and summary of included papers from the systematic review; TBI= traumatic brain injury; SDH= subdural hematoma; ICH= intracerebral hemorrhage; BT= brain tumor; NC= neurocritical care (including TBI, SDH, sICH, BT..); SR= systematic review; MA= meta-analysis; P= prophylaxis; T= therapy; AMSTAR-2 (high/moderate/low/critical low); incl.=included

5.1.3 Quality Assessment

For this systematic review, all included works were assessed for quality using AMSTAR-2. As this validation tool consists of 16 questions, 7 domains are categorized as critical. After completion of AMSTAR-2, for each included systematic review separately, all of them were categorized as critically low in quality.

To provide full transparency, all the obtained results from the completed official AMSTAR-2 protocols are summarized as an overview table and attached in the Appendix 10.4. According to the numbers in the ( ), following this passage, each ( ) is referring to the respective number corresponding with the category of AMSTAR-2, also attached in the Appendix 10.4.

Although all included works adjusted their review scope and inclusion criteria according to the components of PICO (1), only 2 of the 10 systematic reviews partially established a review method prior to protocol development (2) to document any potential and significant deviations from the protocol. Although no clear justification for absent prior review methods were mentioned, all of them obeyed a comprehensive literature search strategy (4) and most of them explained the reasoning for the included study designs (3). Nevertheless, none of the included works provided a list of excluded studies to justify this aspect of the literature search (7), including an exact description of title, author, and publication year, as required by AMSTAR-2. Additionally, it must be mentioned that all the included works performed a study selection in duplicate (5). Regarding study extraction (6) within the literature search, which was also required to be performed in duplicate, only Gigliotti et al. 2021(52) did not fulfill this criterion, as no explicit information addressing this requirement was reported in the systematic review. Only 4 works described the included studies in adequate detail, corresponding with all required AMSTAR-2 subcategories and the remaining 6 systematic reviews were partially accordant to those (8).

Assessing the risk of bias with adequate technique (9) was considered for the respective reviews in dependence of the included works, whether randomized controlled studies were investigated or not, and were assessed in 7 out of 10 included reviews. One review, Walbert et al., 2021(58), did not assess any risk of bias as this review included just studies which were based on the respective American Academy of Neurology (AAN) evidence classification.

Seven included systematic reviews performed a meta-analysis and the majority utilized appropriate statistical methods to combine the results (11). Moreover, 5 of the reviews which performed a meta-analysis, also evaluated the risk of bias whether the individual studies might have influenced the overall conclusions (12).

In contrast, most of the included systematic reviews assessed the risk of bias in the included studies and incorporated this assessment into the discussion or conclusion (13).

Consequently, most reviews provided explanations for the observed heterogeneity among the reported results (14). However, only three studies, Wat et al., 2019(54); Gigliotti et al., 2021(52) and Fang et al., 2022(59), which conducted a meta-analysis, (15) performed an appropriate investigation of publication bias and discussed its potential impact on the results.

None of the included reviews reported information on funding sources. However, all of them disclosed any potential conflicts of interest, including whether they received funding for conducting the review.

More than one critical item did not correspond with the required AMSTAR-2 properties and therefore influenced the overall result in all included systematic reviews leading to a critically low quality rating.

5.1.4 Synthesized Recommendations from the Systematic Review Combined with Guideline Recommendations

Nevertheless, several patterns were identified that aligned with the neurosurgical key categories and were compared with selected guidelines. These patterns formed the synthesized recommendations presented in Table 12. Based on this Table, general recommendations were formulated and used to evaluate the alignment within the MUE.

All the works highlighted the use of a non-enzyme inducing ASM, with the majority suggesting LEV. Furthermore, the most robust evidence was observed in TBI and brain tumor patients resulting in a non-sustained primary prophylaxis. Optimal dosage is still questionable as dosages are estimated to be insufficient, as mentioned in the work of Frontera et al., 2024 (2). Here it was documented that in critically ill patients, higher dosages may be required as 500 mg LEV twice daily may have less than 25% probability of achieving therapeutic levels. Therefore, the inclusion of a dosage recommendation was not feasible and is not mentioned in the following. In general, LEV dosages within the reviewed literature were reported to be between 500 mg to 3000 mg per day but no exact dosage regimes were included.

Although heterogeneity among the reviewed literature was present, the connection of findings with chosen guidelines led to translated synthesized recommendations, which are presented in the following Table.

Neurosurgical indication	Primary/ Secondary prophylaxis (PP/SP)	Systematic Review	Guideline recommendations	Synthesized recommendations
TBI	PP	• No statistic difference considering ePTS vs. lPTS in ASM vs. no ASM(2) • If ASM prophylaxis considered short duration < 7d. recommended	**ACS – The management of TBI(49):** • If considered, use 7 d, not longer • Not recommended in patients without intracranial bleeding or with isolated traumatic SAH	• if starting LEV prophylaxis was considered → limit to 7d
	SP	Not applicable, no data found within the literature search	**DGN(36):** • ideally EEG within 24h after first seizure • if seizure occurred within the acute phase → no indication, stop therapy after acute phase (before discharge or transfer)	• EEG, if EPs then, prolonged LEV therapy suggested • If seizure occurred within acute phase, no prolonged use, restriction to 7 d
SDH	PP	• ePTS and lPTS in aSDH associated with higher incidencece in aSDH than cSDH (55) • in patients with severe aSDH, PP cand be considered, restricted to 7 d	-	• No LEV indication • if starting LEV was considered → limit duration to 7d, if still no seizure occurred
	SP	Not applicable, no data found within the literature search	**DGN(36):** • ideally EEG within 24h after first seizure • if seizure occurred within the acute phase → no indication, stop therapy after acute phase (before discharge or transfer)	• EEG, if EPs, then prolonged LEV therapy suggested • If seizure occurred within acute phase, no prolonged use, restriction to 7 d

Table 9 Synthesized recommendations based on findings from the systematic review and chosen guidelines; TBI= traumatic brain injury; SDH= subdural hematoma; aSDH=acute subdural hematoma, cSDH=chronic subdural hematoma; ACS=American College of Surgeons; DGN=Deutsche Gesellschaft für Neurologie; ePTS=early post traumatic seizure, lPTS=late post traumatic seizure;EEG=electroencephalogram; EPs= epileptiform potentials; LEV=Levetiracetam

Neurosurgical indication	Primary/ Secondary prophylaxis (PP/SP)	Systematic Review	Guideline recommendations	Synthesized recommendations
sICH	PP	• No association of seizure risk reduction in ASM vs. no ASM → no recommendation of ASM(52)	**AHA/ASA Guideline(47):** • No ASM indication	• No LEV indication
	SP	Not applicable, no data found within the systematic review	**DGN(36):** • ideally EEG within 24h after first seizure • if seizure occurred within the acute phase → no indication, stop therapy after acute phase (before discharge or transfer)	• EEG, if EPs, then prolonged LEV therapy suggested • If seizure occurred within acute phase, no prolonged use, restriction to 7 d
BT	PP	• No increase of seizure free survival and reduction	**EANO-ESMO(5):** • no ASM indication	• No LEV indication
	SP	Not applicable, no data found within the literature search	**EANO-ESMO(5):** • ASM treatment indicated after first seizure • prefer LEV or LTG due to efficacy and good tolerability	• LEV treatment indicated
NC	PP	• No routine ASM use, only in high risk patients(60)	-	• No LEV routine use
	SP	• routinely advised	**DGN(36):** • ideally EEG within 24h after first seizure • if seizure occurred within the acute phase → no indication, stop therapy after acute phase (before discharge or transfer)	• EEG, if EPs, then prolonged LEV therapy suggested • If seizure occurred within acute phase, no prolonged use, restriction to 7 d

Table 10 Synthesized recommendations based on findings from the systematic review and chosen guidelines; sICH= spontaneous intracerebral hemorrhage; BT= brain tumor; NC= neurocritical care; AHA/ASA= American Heart Association/American Stroke Association
EANO=European Association of Neuro-Oncology; ESMO=European Society of Medical Oncology; DGN=Deutsche Gesellschaft für Neurologie
EEG=electroencephalogram; EPs= epileptiform potentials; LEV=Levetiracetam; LTG=Lamotrigine

5.2 **Results from the MUE**

A total number of 985 patients were identified during this timeframe. Patients had to be excluded due to the following aspects, which are also illustrated in Figure 4.

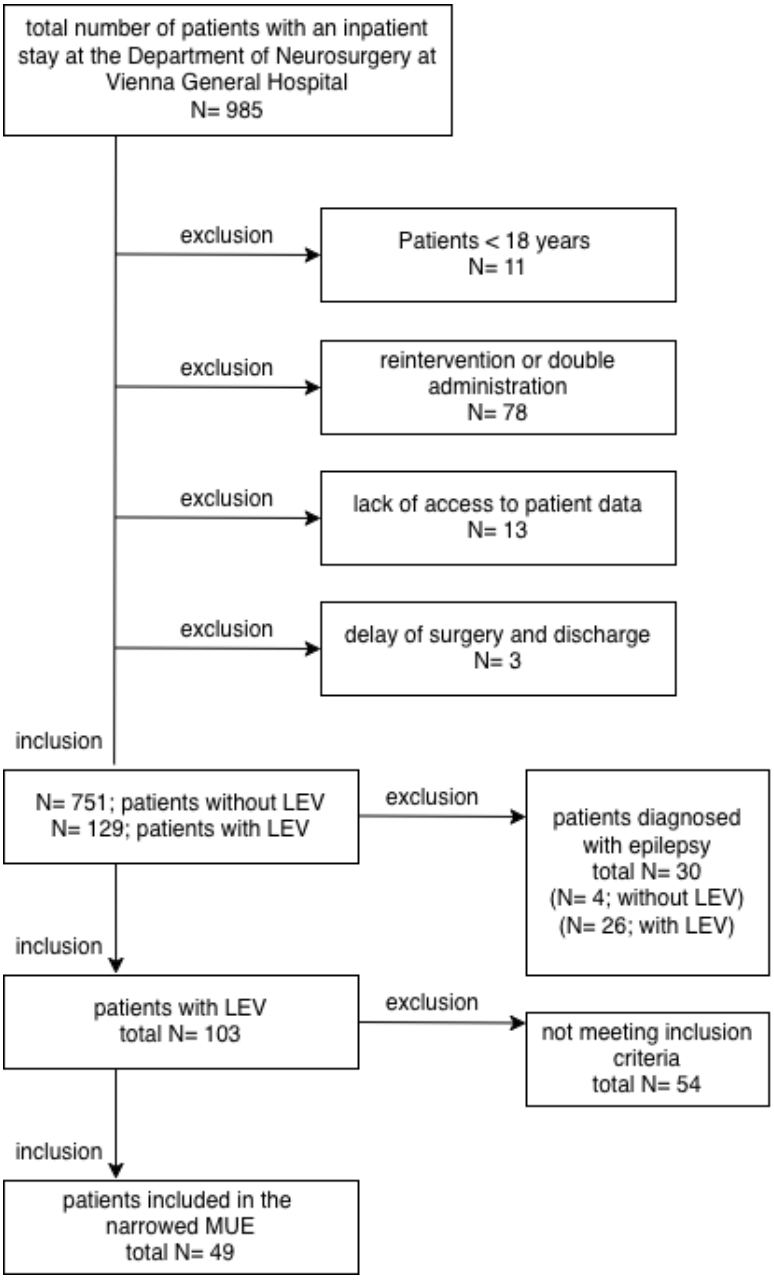

Figure 2 Selection process of the patients in accordance with the presented inclusion criteria and other factors, described in this Figure

Meeting all the inclusion criteria a total of 850 patients were included. Out of these, 103 patients had LEV therapy established without a diagnosis of epilepsy, and 747 patients did not have LEV in their medication list and/or did not receive it during the inpatient stay. From a total identified number of 103 patients who had LEV in their medication list, in 54 patients

(52.4%) the therapy was either established before the inpatient stay or was not well enough documented. In 49 patients (47.6 %) LEV therapy was initiated around the time of neurosurgical admission, as a new-onset therapy. Therefore, 49 cases (47.6%) were included in the narrowed MUE.
Considering the group which had LEV in their medication (n=103), 34 patients (33.0%) received the substance as a new therapy during the general course of the inpatient stay at the Department of Neurosurgery at the Vienna General Hospital. Furthermore, in 15 patients (14.6%) LEV therapy was initiated before transfer to the neurosurgical ward, from another ward or another hospital, but still in relation to the perioperative setting, which were also included in the narrowed MUE.

A detailed MUE could be performed in 49 cases (47.6%) around the neurosurgical intervention. Regarding the remaining 54 patients, LEV therapy was prescribed for longer than one year, or documentation did not correspond with inclusion criteria or was not detailed enough. Additionally, within this group, 3 patients were identified as having LEV therapy initiated during the inpatient stay at the neurosurgical ward at the Vienna General Hospital. Due to the exceeding time frame, outside of the periinterventional setting, those were not included in the narrow MUE, but still had LEV in their medication list.

The following Table presents the obtained results from the MUE considering demographic data such as sex and age, and clinical parameters such as diagnosis.

Characteristics	Value n (%)		
	PP	**SP**	**Total**
	26 (53.1)	23 (46.9)	49 (100)
Age; mean standard deviation	55	56.7	55.8
Minimum	26	21	21
Maximum	83	79	83
Sex n (%)	-	-	-
Female	15 (57.7)	10 (43.5)	25 (51.0)
Male	11 (42.3)	13 (56.5)	24 (49.0)
Diagnosis via ICD-10 classification	-	-	-
C71.9 *malign. neoplasm of meninges, brain unspecified*	1 (3.9)	3 (13.0)	4 (8.2)
C79.3 *Secondary malign. Neoplasm of brain and cerebral meninges*	1 (3.9)	6 (26.1)	7 (14.3)
D32.0 *Benign neoplasm of meninges, cerebral meninges*	4 (15.4)	3 (13.0)	7 (14.3)
D43.0 *Neoplasm of uncertain or unknown behaviour of brain and CNS, brain supratentorial*	2 (7.7)	4 (17.4)	6 (12.2)
D43.2 *Neoplasm of uncertain or unknown behaviour of brain and CNS, brain unspecified*	3 (11.5)	0 (0.0)	3 (6.1)
D43.4 *Neoplasm of uncertain or unknown behaviour of brain and CNS, spinal cord*	0 (0.0)	1 (4.4)	1 (2.0)
G06.0 *Intracranial abscess and granuloma*	1 (3.9)	0 (0.0)	1 (2.0)
I60.9 *Subarachnoid hemorrhage, unspecified*	0 (0.0)	1 (4.4)	1 (2.0)
I62.0 *Nontraumatic subdural hemorrhage, unspecified*	0 (0.0)	1 (4.4)	1 (2.0)
I62.9 *Intracranial hemorrhage (nontraumatic), unspecified*	2 (7.7)	0 (0.0)	2 (4.1)
I67.1 *Cerebral aneurysm, nonruptured*	6 (23.1)	1 (4.4)	7 (14.3)
Q28.2 *Arteriovenous malformation of cerebral vessels*	2 (7.7)	1 (4.4)	3 (6.1)
S06.5 *Traumatic subdural hemorrhage*	2 (7.7)	1 (4.4)	3 (6.1)
T81.1 *Shock during or resulting from a procedure, not elsewhere classified*	1 (3.9)	1 (4.4)	2 (4.1)
No ICD-10 documented	1 (3.9)	0 (0.0)	1 (2.0)

Table 11 Overview of demographic characteristics of study population and clinical parameters obtained from the MUE
PP= primary prophylaxis, SP=secondary prophylaxis
All international classifications of diseases (ICD-10; version 9) derive from the officially accessible description provided by the World Health Organization (WHO)
In one case no ICD-10 classification was documented, as the patient did not underwent any neurosurgical intervention
n (%) is calculated for each column separately

Audited guideline conformity of LEV prescriptions in the perioperative neurosurgical setting are presented in following Figures. Of the 49 cases included in the MUE, only 17 patients (34.7%) were treated in accordance with the synthesized recommendations. In contrast, 32 cases (65.3%) did not align with the synthesized recommendations.

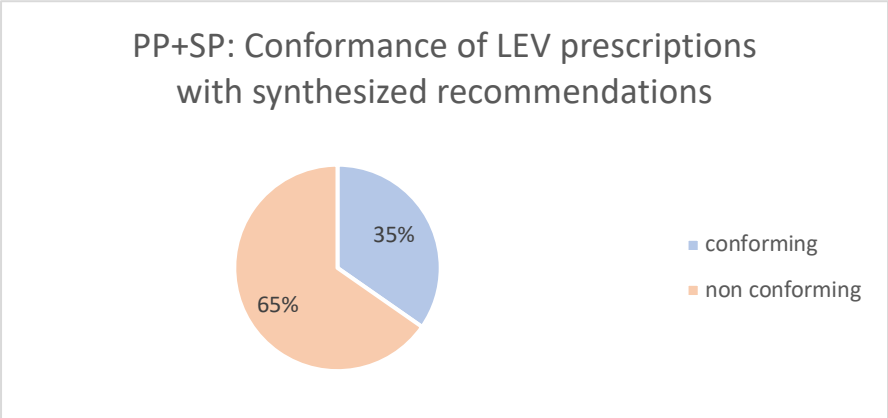

Figure 3 Overview of MUE
LEV conformance with synthesized recommendations, including primary (PP) and secondary (SP) prophylaxis

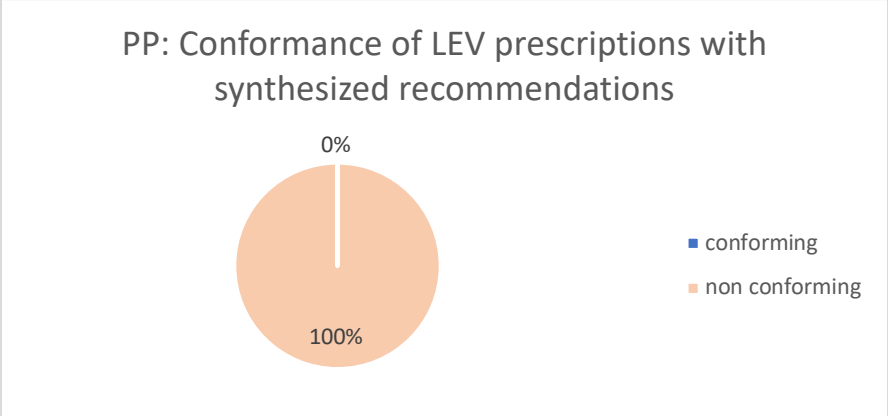

Figure 4 Overview of MUE
Conformance of LEV prescriptions as primary prophylaxis (PP) with synthesized recommendations

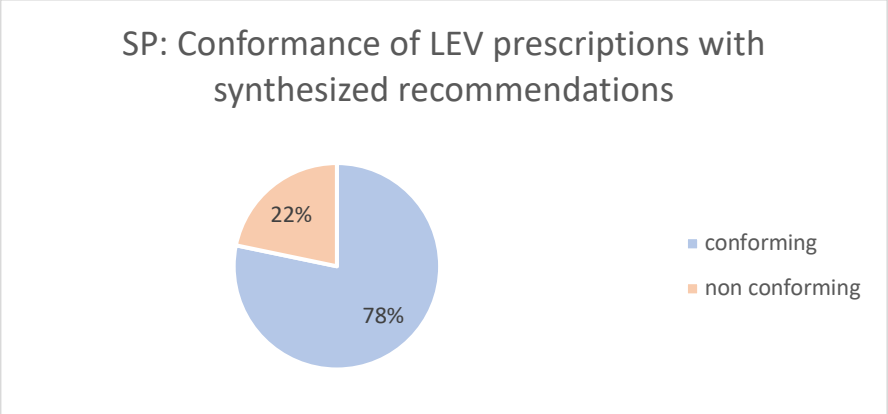

Figure 5 Overview of MUE
Conformance of LEV prescriptions as secondary prophylaxis (SP) with synthesized recommendations

Regarding the initiation of LEV as primary prophylaxis (PP), 26 cases were identified but none of them were consistent with the synthesized recommendations. In contrast, 23 cases involved initiation of LEV as secondary prophylaxis (SP), and in 18 patients (78.3%) the treatment aligned with the recommendations.

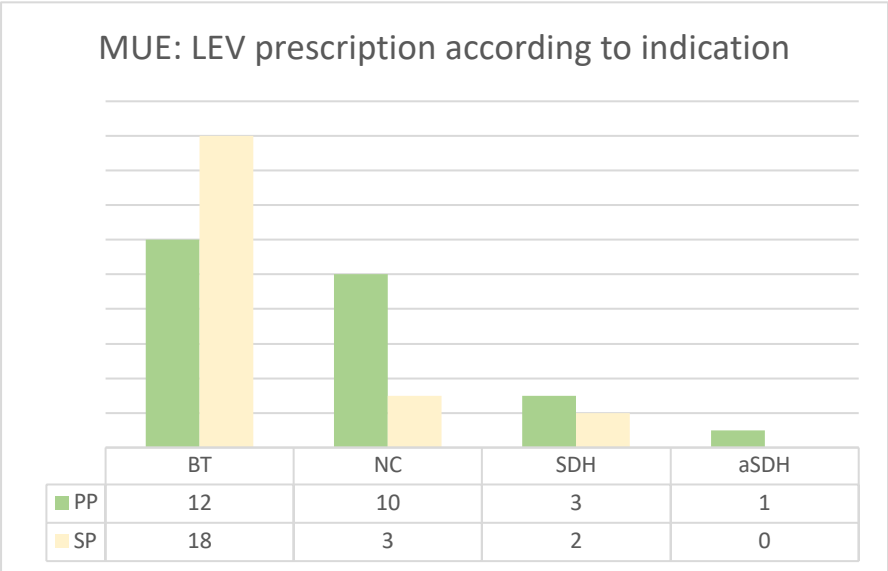

Figure 6 MUE of LEV prescription patterns: primary prophylaxis (PP) vs. secondary prophylaxis (SP) by neurosurgical key categories
BT=brain tumor, NC=neurocritical care, SDH=subdural hematoma, aSDH=acute subdural hematoma

Nevertheless, most of the LEV prescriptions (26 patients), were initiated as primary prophylaxis, which did not comply with recommendations. Most of PP were initiated in the patient group with brain tumors, followed by neurocritical care. As no other key category was suitable for these cases, neurosurgical diagnoses such as aneurysms, non-ruptured aneurysms, arteriovenous malformations or intracranial abscess and granuloma drainage, were included in the NC-group.

In the SP group, patients with brain tumors showed the highest rate of LEV initiation, followed by the NC group.

Regarding discharge management, information on LEV therapy duration was provided in only 12 cases (24.5%), with heterogeneous recommendations documented in the discharge letters. For 5 patients (10.2%) among all 49 cases included in the narrowed MUE, a predefined timeframe for therapy duration and LEV discontinuation was specified.

The following Table provides a detailed overview of the LEV prescriptions, including both therapy duration and dosage regimen within PP and SP group.

Characteristics	Value n (%)		
	PP 26 (53.1)	**SP** 23 (46.9)	**Total** 49 (100)
Any documentation on therapy evaluation for LEV	-	-	-
no	19 (73.1)	18 (78.3)	37 (75.5)
Recommendation for LEV therapy duration/ evaluation in the discharge letter	-	-	-
- Documentation with a defined timeframe	5 (19.2)	0 (0.0)	5 (10.2)
< 7d	1 (3.9)	0 (0.0)	1 (2.0)
< 14d	3 (11.5)	0 (0.0)	3 (6.1)
> 14d	1 (3.9)	0 (0.0)	1 (2.0)
- Evaluation at Neurologist (no timeframe)	0 (0.0)	1 (4.4)	1 (2.0)
- Evaluation at Neurologist in 2 months	0 (0.0)	1 (4.4)	1 (2.0)
- Evaluation at Neurologist in 3 months	0 (0.0)	3 (13.0)	3 (6.1)
- Evaluation at Neurologist in 3-6 months	1 (3.9)	0 (0.0)	1 (2.0)
- Evaluation at Neurologist in 6 months	1 (3.9)	0 (0.0)	1 (2.0)
Information on dosage	-	-	-
Once a day	1 (3.9)	0 (0.0)	1 (2.0)
Twice a day	24 (92.3)	23 (100)	47 (95.9)
Three times a day	1 (3.9)	0 (0.0)	1 (2.0)
Dosage in mg per administration	-	-	-
250 mg	1 (3.9)	0 (0.0)	1 (2.0)
500 mg	20 (76.9)	11 (47.8)	31 (63.3)
750 mg	0 (0.0)	2 (8.7)	2 (4.1)
1000 mg	5 (19.2)	7 (30.4)	12 (24.5)
1500 mg	0 (0.0)	2 (8.7)	2 (4.1)
2000 mg	0 (0.0)	1 (4.4)	1 (2.0)

Table 12 Overview of LEV therapy duration and dosage characteristics
PP= primary prophylaxis, SP=secondary prophylaxis
n (%) is calculated for each column separately

Most LEV prescriptions were not mentioned in the discharge letter regarding a therapy evaluation. Only 12 cases (24.5%) included any documentation of LEV therapy duration, and in 5 patients (10.2%) the documentation specified a restricted time frame for LEV therapy with a clear discontinuation recommendation. All of these belonged to the PP group. Heterogeneous LEV dosing regimens were observed, with 500 mg twice daily being the most common schedule. In one patient (2.0%), LEV was administered three times per day, and in another case (2.0%) it was administered once daily. Within the PP group, a neurologist was consulted in three cases but LEV therapy was continued despite the neurologist's recommendation for discontinuation.

6 Discussion

Patients requiring neurosurgical intervention are at increased risk of experiencing seizures. The use of LEV has become more favorable in this setting not only because of its advantageous pharmacodynamic profile, including a lack of clinically relevant drug-drug interactions, but also because of its pharmacokinetic properties such as rapid bioavailability and immediate seizure suppressant activity.
Although the supporting evidence for primary prophylactic therapy in patients without a prior seizure is limited, it is still practiced during the clinical course. In contrast, actual evidence, and guideline recommendations for ASM after a seizure, as secondary prophylaxis, are better defined.

This thesis aimed to generate recommendations through a systematic review addressing this clinical problem, supplemented by existing guideline recommendations. Subsequently, the concordance between the derived recommendations and guideline adherence was assessed through a retrospective MUE, highlighting discrepancies between the available evidence and clinical practice.

The findings of this systematic review did not allow for the formulation of a single general clinical recommendation, due to substantial heterogeneity arising from the wide range of included indications and neurosurgical conditions. All included systematic reviews were assessed for quality with AMSTAR-2 and were rated as critically low in quality, with each presenting more than one critical flaw and primarily focusing on primary prophylactic use.
Additionally, the available literature is limited by a lack of randomized controlled trials, small study populations, heterogeneous neurosurgical indications, and variability in clinical severity. All these factors are detrimental to the study design and contribute to inconsistent and limited evidence. These limitations highlight the urgent need for well-designed prospective studies with larger sample sizes, a need that has already been acknowledged in several of the included studies. (2, 59, 60)

Across all defined neurosurgical indication subgroups, two included publications investigated on ASM related seizure reduction in the neurocritical care setting, predominantly evaluating primary prophylaxis. Only the systematic review by Jiang et al., 2025(60), evaluated evidence for secondary ASM prophylaxis in relation to existing guidelines. The authors suggest a possible duration for 3 days to two weeks for primary prophylaxis. For secondary prophylaxis, following a postoperative seizure, ASM therapy for 3 months to one year may be considered. Thus, the optimal duration of secondary ASM prophylaxis across multiple neurosurgical indications remains unclear. This uncertainty may

contribute to variability in clinical practice and result in a prescription gap. Furthermore, this uncertainty may lead to unnecessary prolonged use of both primary and secondary prophylaxis beyond the evidence-based durations. Even if Jiang et al., 2025(60) state that secondary seizure prophylaxis is routinely advised, it is important to consider the timing of seizure occurrence and whether it falls within the acute period. In such cases, an EEG should be performed to assess for epileptiform discharges to determine whether prolonged ASM therapy is indicated. These recommendations would likely align with those of the DGN(36), assuming comparable patient populations. Proper documentation is essential to optimize therapy duration and to prevent unnecessary prolonged ASM use, particularly given the limited current evidence.

Another major gap in the available literature concerns the optimal dosage and treatment duration, as no precise recommendations have been defined. Moreover, the systematic review failed to establish a definitive dosing regimen. For instance, Frontera et al., 2024(2) report that 500 mg of LEV administered twice daily may have less than a 25% probability of achieving therapeutic serum levels in neuro-critically ill patients, which raises concerns that the doses used in many studies may have been subtherapeutic. Consequently, higher doses may be required to achieve clinical efficacy.
Due to the lack of established recommendations, the dosing regimen may still be questioned based on this finding, especially since the MUE results show that 500 mg LEV twice daily was the most frequently prescribed dose. (63.3%)
However, it remains unclear whether these findings can be generalized to the broader neurosurgical population, as not only neuro-critically ill patients were included in the MUE.
Considerable variations exist among the studies, resulting in uncertainty regarding optimal clinical use and potentially contributing to inconsistent treatment practices.

Overall, the supporting evidence for LEV use as primary prophylaxis remains limited, as most available data concerns PHT, likely due to its longer history of clinical use and data availability.
However, PHT is associated with less favorable pharmacodynamic and pharmacokinetic properties compared with LEV, resulting in a higher risk of drug-related adverse effects. The cautious use of PHT and the recommendation of LEV as a suitable alternative have been documented in several studies(54).While the study by Pourzitaki et al., 2016(56) suggests that prophylactic LEV may reduce early postoperative seizures in patients with brain tumors and may be superior to PHT or valproate in this context, the supporting evidence remains weak and insufficient.

In contrast, the EANO/ESMO guidelines(5) specify that ASM should not be used prophylactically in patients with brain tumors who have not experienced seizures. However, if ASM is prescribed in patients prior to seizure, a non-enzyme inducing agent such as LEV should be used.(5)

Methodological weaknesses across studies limit the robustness and validity of the current clinical evidence and may contribute to inconsistencies in clinical practice, including uncertainty regarding optimal treatment duration, which may result in a prolonged ASM treatment.
This pattern is also reflected in the MUE, where more than 50% of included patients received LEV as primary prophylaxis, particularly among patients with brain tumors, despite EANO/ESMO guideline recommendations.(5)
The results from the PP group show that the majority of patients with a neurosurgical indication of brain tumor received LEV as PP, despite clear guideline recommendations against this practice. Of the 26 patients in the PP group, 12 (46.2%) had a brain tumor diagnosis. Only 3 (25%) of these 12 patients had discharge letters that clearly documented LEV therapy and provided recommendations for discontinuation or further evaluation. The remaining patients had no documentation regarding LEV therapy, neither as PP i.e. in the absence of a seizure, nor as part of an evaluation for ongoing treatment. This lack of recommendations suggests that a seizure may have occurred, which could potentially distort the interpretation of the decision to continue LEV therapy.

These conflicting findings underscore the need to critically address prolonged prophylactic treatment in the absence of seizures.
Additionally, two independent studies by Afshari et al., 2017(65) and Ambrosi et al., 2017(1) state that ASM use for postoperative neurosurgical seizure prophylaxis reduces only the risk of early seizures within 7 days after intervention. Beyond this early postoperative period, continuation of ASM did not demonstrate any significant effect on preventing late-onset seizures.(1) In any case, the evaluation of LEV therapy prolongation appears sensible although clinical data remains limited.

Moreover, it is also important to critically address the SP use of LEV when the first seizure occurs during the perioperative setting and whether prolonged therapy is indicated, or whether the seizure itself it may be considered symptomatic, implying the need for therapy evaluation and LEV discontinuation.
In the prospective study by Herzig-Nichtweiß et al., 2023(3), it was confirmed that even in the presence of structural brain pathology, most acute symptomatic seizures have a low

risk of subsequent unprovoked seizures, and that patients were treated with ASM for longer than recommended. However, the occurrence of unprovoked seizures was independent of treatment duration, supporting restricted ASM use limited to the acute phase of the underlying disease.(3) Nevertheless, it should be noted that perioperative neurosurgical patients were underrepresented in this cohort.

The DGN highlights within their guideline *Erster epileptischer Anfall und Epilepsien im Erwachsenenalter*(36) the targeted use of ASM for symptomatic seizures. The recommendation is EEG monitoring within 24h after the first seizure, which was not performed in all patients in the SP group. Moreover, ASM initiated after an acute symptomatic seizure, as SP, should be discontinued at discharge or transfer due to low risk of unprovoked seizure recurrence.

Nevertheless, it was counted as concordant with the recommendations, because therapy with LEV was initiated after a seizure in the brain tumor group. Otherwise, concordance with synthesized recommendations would have been poorer.

As this medication use evaluation classified all patients with a seizure during the perioperative setting as secondary prophylaxis, and therefore considered the brain tumor group as correspondent with the guidelines, it still needs to be mentioned that critical evaluation and proper documentation of the seizure, at least in the discharge summary, could optimize the neurological perspective and influence the duration of seizure-suppressive medication.

EANO/ESMO(5) also address this issue and mention the transient ASM treatment. Thus, therapeutic interventions against brain tumors such as surgery, radiotherapy, and chemotherapy, contribute to seizure control. Especially after surgery, if near-total tumor resection is achieved, ASM could be tapered within weeks if no tumor recurrence is observed.

Furthermore, three cases were identified in which neurology was consulted within this PP group. Despite this, the patients were discharged on LEV although the neurology consultation did not support the continued use of ASM and recommended discontinuation. Additionally, no documentation of this recommendation or any specific information about LEV use as PP was included in the discharge summaries. This poses a potential problem for the subsequent course of care, as it may impede evaluation at a later point and make potential deprescribing more difficult because essential clinical information is missing.

In addition, this may also represent a care-transition issue when patients are admitted to another hospital or to a community-based physician, since discharge summaries are accessible, but specialty consultation recommendations are not.

The MUE further demonstrated variability in prescribed dosages and a lack of documented treatment durations within the small patient cohort (n=49), highlighting heterogeneous and potentially insecure prescribing patterns.
Similar variability has been reported in one study from Pascarella et al., 2025(66), an online cross-sectional survey from Italy which identified significant differences in decision-making regarding ASM initiation and discontinuation in neurosurgical patients. Additionally, this study also highlights the low rate for neurologists' involvement in ASM management (48.7%), which is comparable to the practice patterns observed in the MUE.

Although there is already an established clinical pharmacy service at the Department of Neurosurgery at the Vienna General Hospital, and clinical pharmacists participate in interdisciplinary rounds, this issue still leaves room for optimization.
On the one hand, this issue may be explained by heterogeneous and limited available evidence, and on the other hand it may result from the individualized initiation of LEV therapy by neurosurgeons, especially as primary prophylaxis. This contributes to heterogeneous clinical practice. An attempt to develop an interdisciplinary approach to LEV use in the perioperative setting may help optimize several aspects.
It may help to shorten the prolonged prescription of LEV as PP or SP and potentially prevent long-term therapy with LEV. Involving neurologists and establishing a standard protocol could optimize this process and lead to more appropriate dosing, as well as support proper tapering and therapy discontinuation when it is not needed.
An available standard could also support physicians in decision-making and facilitate medication reviews by clinical pharmacists, resulting in recommendations being more likely accepted if the involved healthcare professionals are more sensitized to this topic.
Moreover, it may help ensure clear documentation in discharge summaries and prevent interface problems when important information is missing in the outpatient setting such as whether therapy initiation was as PP or SP and the timing of seizure occurrence (pre- or postoperative). These findings may be relevant for further physician appointments.

Nevertheless, several limitations of this work need to be mentioned, including the retrospective design of the MUE. Due to its retrospective character, it is associated with incomplete and inconsistent documentation, limiting the inclusion of patients, and resulting in a small sample size (n=49). Furthermore, the lack of follow-up data after hospital discharge prevents assessment of ongoing ASM use and may underestimate prolonged and non-evidence-based treatment. Further studies with a prospective design and follow-up at multiple time points are needed.

7 Abstract

Title: Systematic Review and Medication Use Evaluation of Levetiracetam Prescriptions in the Perioperative Neurosurgical Setting

Background: Neurosurgical conditions may be associated with an increased perioperative seizure risk. Due to its favorable pharmacological profile, LEV is often used in the perioperative setting, including as primary seizure prophylaxis in patients without a prior seizure, despite limited supporting evidence.

Objectives: This study aimed to synthesize evidence-based recommendations for the perioperative use of newly initiated LEV therapy in the neurosurgical setting. Furthermore, the concordance between these recommendations and clinical prescription patterns was evaluated using a monocentric retrospective data analysis to assess potential non-evidence based prolonged prescribing.

Methods: A systematic review was conducted to identify relevant literature which was audited alongside guidelines recommendations, resulting in indication-specific synthesized recommendations. These were evaluated for concordance through a retrospective MUE conducted at the Department of Neurosurgery of the Vienna General Hospital.

Results: Within the systematic review, no uniform recommendation for the perioperative use of LEV could be identified. Therefore, an indication-specific differentiation supplemented with clinical guidelines was chosen. Primary prophylaxis in patients without a prior seizure was not supported by the literature or by guidelines. Within the retrospective MUE, primary prophylaxis was initiated in 26 patients (53.1%). Recommendations regarding therapy duration were documented in only 5 cases (19.2%), and therapy evaluation in 2 cases (7.7%). Secondary prophylaxis was administered in 23 patients (46.9%), although no explicit recommendations on therapy duration were documented, therapy evaluation was recommended in 5 cases (21.7%). The overall concordance with the synthesized recommendations was low (34.7%), with the highest concordance observed in secondary prophylaxis among patients with brain tumors (78%). These findings suggest potentially avoidable prolonged LEV prescriptions, especially for primary prophylaxis.

Conclusions: The use of LEV in the perioperative neurosurgical setting is not evidence based regarding primary prophylaxis. The findings highlight the need for standardized and more indication-specific recommendations as well as a structured reevaluation strategy to prevent long-term prescriptions.

8 Zusammenfassung

Titel: Systematische Literaturübersicht und Arzneimittelverordnungsanalyse zu Levetiracetam-Verordnungen im perioperativen neurochirurgischen Umfeld

Hintergrund: Neurochirurgisch interventionsbedürftige Erkrankungen können mit einem erhöhten perioperativen Anfallsrisiko assoziiert sein. Aufgrund seines günstigen pharmakologischen Profils wird LEV zunehmend im perioperativen Setting eingesetzt, auch als Primärprophylaxe bei Patienten ohne stattgehabten Anfällen, trotz limitierter Evidenzlage.

Zielsetzung: Ziel war die systematische Erfassung evidenzbasierter Empfehlungen zum perioperativen Einsatz von neu initiierten LEV Therapien in der Neurochirurgie. Außerdem wurde der Übereinstimmungsgrad dieser Empfehlungen mit der klinischen Praxis anhand einer monozentrischen retrospektiven Datenauswertung bewertet, um das Potenzial nicht evidenzbasierter prolongierter Verordnungsdauer aufzuzeigen.

Methoden: Ein systematisches Review identifizierte relevante Literatur, welche durch Leitlinien ergänzt wurde, um indikationsspezifisch synthetisierte Empfehlungen zu generieren. Anschließend wurden diese mittels einer retrospektiven MUE an der Abteilung für Neuro-chirurgie des Universitätsklinikums AKH Wien hinsichtlich Übereinstimmungsgrad ab-geglichen.

Ergebnisse: Das systematische Review konnte keine einheitliche Empfehlung für den perioperativen Einsatz von Levetiracetam liefern, weshalb eine indikationsspezifische Differenzierung erforderlich war. Diese wurde aus den Ergebnissen des systematischen Reviews generiert und durch entsprechende Leitlinien ergänzt. Der Einsatz als Primärprophylaxe, bei Patienten ohne stattgehabten Anfall, konnte weder durch Leitlinien noch durch die Literatur gestützt werden. In der retrospektiven Datenanalyse wurde bei 26 Patienten (53,1%) eine Primärprophylaxe etabliert. Eine definierte Therapiedauer war im Entlassungsbrief jedoch nur bei 5 (19,2%) dokumentiert und eine Therapieevaluation nur in 2 Fällen (7,7%). Im Gegensatz dazu erhielten 23 Patienten (46,9%) eine Sekundärprophylaxe. In keinem Fall wurde eine exakte Empfehlung zur Therapiedauer festgehalten, bei 5 Patienten (21,7%) war hingegen eine Therapieevaluation im Verlauf im Entlassungsbrief vermerkt.

Insgesamt zeigte sich eine geringe Leitlinienkonformität (34,7%) mit der höchsten Übereinstimmung als Sekundärprophylaxe bei Patienten mit Hirntumoren (78%). Dies weist auf potenziell vermeidbare prolongierte Levetiracetam-Verordnungen hin, vor allem bei Patienten, bei denen Levetiracetam als Primärprophylaxe zum Einsatz kam.

Schlussfolgerungen: Der Einsatz von LEV im perioperativen neurochirurgischen Umfeld erfolgt häufig ohne klare evidenzbasierte Grundlage, vor allem im Rahmen der Primärprophylaxe. Die Ergebnisse unterstreichen den Bedarf an standardisierten,

indikationsspezifischen Empfehlungen sowie auch strukturierten Reevaluationsstrategien, um nicht indizierte Langzeitverordnungen zu vermeiden.

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10 Appendix

10.1 Full Search Strings for PubMed and EMBASE

PubMed:

(Neurosurgery) AND (seizure) AND (levetiracetam*)*

- ***243 Hits***

(Neurosurgery) AND (seizure*) AND (levetiracetam*) AND (therapy OR prophylaxis)*

- ***280 Hits***

(*neurosurgery* OR neurosurgical* OR brain surgery*) AND (perioperative OR preoperative OR intraoperative OR postoperative) AND (seizure OR seizures) AND levetiracetam AND (prophylaxis OR prevention OR therapy OR treatment)*

- ***86 Hits***

For the final search in PubMed following search term string was used:

(((Neurosurgery) AND (seizure*) AND (levetiracetam*) AND (therapy OR prophylaxis)) OR ((Neurosurgery*) AND (seizure) AND (levetiracetam*))) OR ((neurosurgery* OR neurosurgical* OR brain surgery*) AND (perioperative OR preoperative OR intraoperative OR postoperative) AND (seizure OR seizures) AND levetiracetam AND (prophylaxis OR prevention OR therapy OR treatment))*

– **322 Hits**

EMBASE:

'neurosurgery' AND 'seizure' AND 'levetiracetam'

– ***2157 Hits***

('levetiracetam'/exp OR 'levetiracetam') AND ('neurosurgery'/exp OR 'neurosurgery') AND ('seizure'/exp OR 'seizure')

- ***2788 Hits***

(neurosurgery OR neurosurgical* OR brain) AND surgery* AND (perioperative OR preoperative OR intraoperative OR postoperative) AND (seizure OR seizures) AND levetiracetam AND (prophylaxis OR prevention OR therapy OR treatment)*

- ***723 Hits***

(('levetiracetam'/exp OR 'levetiracetam') AND ('convulsion'/exp OR 'convulsion') AND ('perioperative period'/exp OR 'perioperative period') AND ('neurosurgery'/exp OR 'neurosurgery') OR 'neurosurgery'/exp OR 'neurosurgery') AND ('perioperative period'/exp OR 'perioperative period') AND ('seizure'/exp OR 'seizure') AND ('levetiracetam'/exp OR 'levetiracetam')

-520 Hits

For the final search in EMBASE following search term string was used:

('neurosurgery' AND 'seizure' AND 'levetiracetam') OR (('levetiracetam'/exp OR 'levetiracetam') AND ('neurosurgery'/exp OR 'neurosurgery') AND ('seizure'/exp OR 'seizure')) OR ((neurosurgery OR neurosurgical* OR brain) AND surgery* AND (perioperative OR preoperative OR intraoperative OR postoperative) AND (seizure OR seizures) AND levetiracetam AND (prophylaxis OR prevention OR therapy OR treatment)) OR ((('levetiracetam'/exp OR 'levetiracetam') AND ('convulsion'/exp OR 'convulsion') AND ('perioperative period'/exp OR 'perioperative period') AND ('neurosurgery'/exp OR 'neurosurgery') OR 'neurosurgery'/exp OR 'neurosurgery') AND ('perioperative period'/exp OR 'perioperative period') AND ('seizure'/exp OR 'seizure') AND ('levetiracetam'/exp OR 'levetiracetam'))*

-2919 Hits

After filter Setting:

AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND ([english]/lim OR [german]/lim) AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [2010-2025]/py

- 34 Hits

10.2 Template: Study Summaries for the Systematic Review

Title capitalization follows the respective citation style and the original publications.

Indication	**Traumatic Brain Injury (TBI)**
Title	**The Effectiveness of Antiepileptic Medications as Prophylaxis of Early Seizure in Patients with Traumatic Brain Injury Compared with Placebo or No Treatment: A Systematic Review and Meta-Analysis**
Author	Wilson et al.
Year	2018
Study Design	Systematic Review and Meta-Analysis
Included Studies	16
Sample Characteristics Incl./Excl. Criteria	**Incl.:** studies which allowed grouping because of the comparison of same factors **Excl.:** studies published before 1970, articles with inhomogeneous data
Research questions	Efficacy of LEV vs. PHT vs. Placebo for 1.) ePTS and 2.) lPTS prophylaxis
Endpoints	Incidence ePTS (< 7 days after TBI) lPTS (>7 days after TBI)
Timing of intervention	Administration of ASM/Placebo early after TBI
Duration of intervention	No specific information about duration mentioned
Dosage of ASM	No specific information about dosage given
Quality assessment	Categorization as level A, B or C according to the methods of the American Heart Association/American Stroke Association, the aggregate quality of evidence for each of the 4 comparison was assigned with Grading of Recommendations Assessment, Development and Evaluation system.
Follow Up	Heterogenous follow up among studies, but never > 2 years
Conclusions	1.) No difference between LEV or PHT for ePTS in severe TBI (as presented in Khan et al.) 2.) lPTS no significant differences for LEV vs. PHT vs. Placebo could be made
Recommendations	For ePTS prevention PHT and LEV are comparable efficient → in concordance with Brain Trauma Foundation (BTF) guidelines that do not support one substance over the other; additionally, regarding practice side-effect and therapeutic index LEV over PHT favored
Limitations	No specific differences in lPTS development if LEV /PHT/Placebo treated Conclusions derive from heterogenous data, majority is retrospective and underpowered to detect a significant difference in seizure prevention efficacy. Heterogeneity regarding duration of treatment and FU. Regarding comparison of LEV vs. Placebo for lPTS prevention Peart et al. analyzed 38 patients and Klein et al. analyzed 126 patients, but both included as well pediatric population! Small studies were also underpowered to detect a difference in the LEV prevention efficacy. Regarding lPTS development patients receiving LEV vs. Placebo were observed in two studies, with small sample size, follow up was two years but one study lost 20.6% follow up resulting in decreased statistical power.

Indication	**Traumatic Brain Injury (TBI)**
Title	**The Effectiveness of Antiepileptic Medications as Prophylaxis of Early Seizure in Patients with Traumatic Brain Injury Compared with Placebo or No Treatment: A Systematic Review and Meta-Analysis**
Author	Wat et al.
Year	2019
Study Design	Systematic Review and Meta-Analysis
Included Studies	9
Sample Characteristics Incl./Excl. Criteria	**Incl.:** studies including at least one of the following drugs PHT, LEV, VPA, CBZ, a placebo or no prophylaxis control arm, report of efficacy of ASM for prophylaxis or ePTS, Clinical Trials and comparative observational studies **Excl.:** case reports, case series, systematic reviews, meta-analyses, non-human studies, and non-English language studies, Brain injury from other causes craniotomies were excluded
Research questions	Preventive usefulness of any antiseizure medication in TBI management
Endpoints	usefulness of any antiseizure medication in TBI management as prophylaxis
Timing of intervention	Initially within 24h of injury in most studies
Duration of intervention	Majority administered ASM for 7 days
Dosage of ASM	No exact information about exact dosage is given
Quality assessment	RCT → Cochrane risk of bias 2 tool (Rob2) Observational studies → Newcastle-Ottawa Scale (NOS)
Follow Up	No specific information about follow up
Conclusions	No significant differences among ASM, no outperformance of a substance with respect to efficacy, PHT is the most studied drug, for LEV there is fewer data available. No difference found between treatment with PHT and LEV. In observational studies modest benefit of ASM as prophylaxis in ePTS in patients with TBI and lack of convincing evidence of ASM effectiveness as prophylaxis of ePTS
Recommendations	Observational studies tend to observe a significant protective effect between ASM and ePTS but results from RCT on PHT did not reach statistical significance. Modest evidence of PHT in risk reduction of ePTS→ physicians should assess whether overall benefit outweighs the known treatment complications
Limitations	Only one included study which investigates LEV as ASM, no dosage mentioned, no subgroup analysis could be performed. Seldom TBI severity stratification among studies, leading to difficulties when comparing results.

Indication	**Traumatic Brain Injury (TBI))**
Title	**Guidelines for Seizure Prophylaxis in Adults Hospitalized with Moderate-Severe Traumatic Brain Injury: A Clinical Practice Guideline for Health Care Professionals from the Neurocritical Care Society**
Author	Frontera et al.
Year	2024
Study Design	Systematic Review and Meta-Analysis with Guideline Development
Included Studies	33
Sample Characteristics Incl./Excl. Criteria	**Incl.:** hospitalized Adults (>18 years of age) with moderate-severe TBI (SAH, SDH or EDH, Contusion, ICH, intraventricular hemorrhage, skull fracture), without seizure history prior to ASM **Excl.:** patients with history of seizure, epilepsy, ASM therapy prior to TBI, pediatric publications, case series, nonhuman studies, studies in other language than English
Research questions	1.) use of ASM vs. no ASM in patients with moderate-severe TBI and no history of clinical or electrographic seizures? 2.) if ASM utilized is LEV or PHT preferred? 3.) Duration short vs. long prophylaxis (< 7 days vs. > 7 days)
Endpoints	Early seizures, Late seizures, Adverse events, Mortality, Functional outcomes (e.g. neurologic function)
Timing of intervention	In between 24-48 hours after admission, or before diagnosis
Duration of intervention	short prophylaxis < 7 days long prophylaxis > 7days
Dosage of ASM	No clear recommendation
Quality assessment	GRADE
Follow Up	Early seizures observed until day 7 late seizures observed between 30 days and 6 months after discharge
Conclusions	1.) No statistic significant difference considering early and late seizures, unwanted adverse events, mortality 2.) No significant difference for early seizures or mortality. LEV has better pharmacodynamic profile and less unwanted adverse events. If ASM is considered, LEV should be preferred. 3.) No clear advantages of long prophylaxis (>7 days). Preferred recommendation to consider short prophylaxis (< 7 days) to avoid potentially negative cognitive effects
Recommendations	1.) No statistic significant difference considering early and late seizures, unwanted adverse events, mortality 2.) Prefer LEV over PHT 3.) If ASM used, short duration < 7 days in comparison to long duration > 7days
Limitations	Included studies with low quality, heterogeneity in dosage, definition of patient groups, definitions of TBI, inclusion criteria, different time points and methods for evaluating early and late seizures, data of functional and cognitive outcomes are limited

Indication	**Subdural Hematomas (SDH)**
Title	**A systematic review of epileptic seizures in adults with subdural hematomas**
Author	Won et al.
Year	2017
Study Design	Systematic Review
Included Studies	24
Sample Characteristics Incl./Excl. Criteria	**Incl.:** Human based studies, epileptic seizures in patients with SDH **Excl.:** studies on pediatric patients, language other than English, redundant data or deficient-insufficient disaggregation to identify the incidence or risk factor of epileptic seizure in SDH
Research questions	1.) Incidence of early/late post traumatic seizures (e/lPTS) in acute vs. chronic types 2.) what are risk factors for ePTS and lPTS in SDH 3.) evidence for prophylactic ASM use in SDH
Endpoints	Incidence of ePTS and lPTS Risk factors for seizures ASM vs. no ASM as prophylaxis
Timing of intervention	no clear uniformed definition
Duration of intervention	No exact information about duration given
Dosage of ASM	No information about dosage in this work given
Quality assessment	No exact information provided
Follow Up	Heterogenous data, up to three years, but no exact data presentation
Conclusions	1.) aSDH associated with high incidence of PTS → ePTS in aSDH 28% and in patients with cSDH 10% Incidence of lPTS in aSDH was 43% within 2 years of follow up cSDH 5.3% within 3 years follow up→ indicating for a lower risk of developing epilepsy Overall incidence of ePTS and lPTS higher in patients with aSDH than cSDH 2.) risk factor for PTS in aSDH→ preoperative and 24h post operative, low GCS score and craniotomy cSDH risk factors→ alcohol abuse, change of mental status, previous stroke, and haematoma density on the CT 3.) in patients with severe aSDH the prophylactic ASM use can be considered but for a limited and short time, e.g. 1 week In patients with cSDH → valuation of ASM prophylaxis individually based on cumulative risk factors
Recommendations	See conclusions, as paper does not make any specific recommendation
Limitations	Risk of bias, as majority of the studies were retrospective, reporting was heterogeneous especially considering definitions of early vs. late studies, no standardization of timing/duration/dosage given Variability in sample size and lack of RCTs

Indication	**Spontaneous ICH (sICH)**
Title	**A Systematic Review and Meta-Analysis of Antiepileptic Prophylaxis in Spontaneous Intracerebral Hemorrhage**
Author	Gigliotti et al.
Year	2021
Study Design	Systematic Review and Meta-Analysis
Included Studies	7
Sample Characteristics Incl./Excl. Criteria	**Incl.:** spontaneous ICH (sICH), prophylactic use LEV vs. no ASM after sICH onset, adults > 18 years of age **Excl.:** prior ASM use in their history, other ASM use than LEV, non English-language, studies with pediatric population
Research questions	1.) LEV vs. no ASM as prophylaxis for seizure prevention 2.) LEV vs. no ASM considering functional outcome 3.) LEV vs. no ASM regarding mortality outcome
Endpoints	1.) Seizure events 2.) Functional status 3.) Mortality
Timing of intervention	No exact information about discontinuation given
Duration of intervention	No exact information about duration given
Dosage of ASM	No information about dosage in this work given
Quality assessment	GRADE-Method
Follow Up	From seven included studies, five had 90 days follow up, and from two studies follow up was no available
Conclusions	1.) No association regarding reduction of seizure risk between LEV prophylaxis vs. no ASM 2.) LEV prophylaxis was associated with worse functional outcome 3.) Trend to decrease in mortality observed in patients treated with LEV but not statistically significant compared to the group without ASM
Recommendations	Orientation and supportive finding coping with the guidelines (e.g. American stroke association 2015) without recommendation of ASM prophylaxis in spontaneous ICH
Limitations	Quality of evidence is overall poor due to incoherent data, retrospective design of the studies and variability among data and outcome → limits to combine studies together in the meta-analysis

Indication	Brain Tumor (BT)
Title	**Efficacy and safety of prophylactic levetiracetam in supratentorial brain tumour surgery: a systematic review and meta-analysis**
Author	Pourzitaki et al.
Year	2016
Study Design	Systematic Literature Review and Meta-Analysis
Included Studies	12
Sample Characteristics Incl./Excl. Criteria	**Incl.:** observational studies (pro- and retrospective), one RCT, adults with brain tumors undergoing biopsy or craniotomy and LEV administration in perioperative course as prophylaxis, comparison of LEV administration vs. no ASM /placebo or other ASM **Excl.:** patients under age of 18 years, pregnancy, breast-feeding, craniotomy for disease other than brain tumor, severe co-morbidities (including renal and liver failure)
Research questions	Efficacy (appearing or not of seizure or reduction of seizure appearance) and safety of prophylactic LEV use in brain tumor patients
Endpoints	Efficacy (appearing or not of seizure or reduction of seizure appearance) and safety of prophylactic LEV use in brain tumor patients
Timing of intervention	Preoperative period: start of treatment until time of surgical intervention Postoperative period: 1.) early postoperative period → 48h after intervention 2.) late postoperative period → 48h till 4 weeks postoperatively 3.) late observation period → 4 weeks postoperatively till completion of the protocol
Duration of intervention	7 days till 12 months
Dosage of ASM	LEV administration i.v. and oral, dosage between 500-3000 mg daily
Quality assessment	Cochrane Risk of Bias Tool
Follow Up	3, 6 and 12 months
Conclusions	Efficacy and safety of LEV use is superior to PHT/VPA (fewer seizure occurrence and side effects among LEV in comparison to PHT)
Recommendations	LEV seems to be more effective in postoperative seizure control, more well-designed studies are necessary
Limitations	Small number of included trials impedes data extractions regarding incidence of seizures through different study periods, blinding data is missing, various dosage regimen among various included studies; only one study investigated LEV vs. no ASM for 6 months after surgery → LEV prophylaxis was not a predictor of seizure occurrence, although the regression analysis indicated a slight seizure risk reduction after LEV administration. Low 30 days seizure incidence after surgery (2.4% LEV vs. 0% no ASM)

Indication	**Brain Tumor (BT)**
Title	**SNO and EANO Practice Guideline Update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors**
Author	Walbert et al.
Year	2021
Study Design	Systematic Review
Included Studies	37
Sample Characteristics Incl./Excl. Criteria	**Incl.:** adult patients with brain tumors related to treatment for seizure or prophylaxis **Excl.:** Trials with less than 20 participants
Research questions	patients with newly diagnosed primary or metastatic brain tumors without experienced seizure ASM vs. no prophylaxis 1.) increase on seizure free survival and reduce first seizure frequency within 6 months from diagnosis 2.) patients undergoing neurosurgical treatment (craniotomy or biopsy) perioperative ASM vs. no prophylaxis 2a.) prolong time to seizure occurrence 2b.) reduce frequency of first seizure 14 days after surgery 3.) 3a.) treatment with VPA or other ASM (either as prophylaxis or following a seizure) in comparison to any other ASM increase the progression-free or overall survival 3b.) more favorable side effect profile in ASM treatment with modern ASM or enzyme inducing antiepileptic drug (EIAED)
Endpoints	Seizure free survival, overall survival, first seizure frequency, Seizure risk reduction in early post operative setting
Timing of intervention	Different modalities in relation to the research questions; starting with diagnosis; post-surgical intervention
Duration of intervention	Different time points according to research questions, 14 days post intervention, 6 months from diagnosis
Dosage of ASM	No specific information about dosage given
Quality assessment	American Academy of Neurology (AAN) therapeutic and causation study classification schemes
Follow Up	Different follow ups according to research questions
Conclusions	ASM are not effective in primary seizure prophylaxis in patients with newly diagnosed brain tumors without experienced seizure 1.) ASM prophylaxis is not likely preventive in increasing the seizure free survival and reducing the frequency of seizures at 6 months from diagnosis 2a.) Patients with brain tumors who underwent surgery ASM possibly not effective in overall seizure reduction 2b.) ASM prophylaxis possibly not effective in seizure reduction following 14 days past intervention 3a.) lack of high evidence level in general but VPA or LEV does not increase progression-free or overall survival 3b.) Use of LEV in patients with brain tumors is well tolerated, prevention of early postoperative seizures within seven days of surgery is comparable to previous studies with first ASM-generation
Recommendations	1.) no ASM prescription in these groups of patients 2a.) 2b.) insufficient evidence for ASM recommendation as seizure risk reduction in the peri- and postoperative period overall and 14 days following surgical intervention 3a.) No effect of ASM treatment in overall seizure reduction → tapering and ASM discontinuation of ASM after first

	postoperative week is appropriate 3b.) prefer LEV prescription over other ASM due to less side-effects
Limitations	Lack of data and limits to detect higher risk subpopulation e.g. based on tumor location, molecular features etc. that might benefit from prophylactic ASM → one study suggested a higher seizure occurrence in patients with low-grade tumors, but data is insufficient for prophylactic ASM suggestion, methodological weakness across studies hinders practice of evidence-based medicine→ need for more randomized trials

Indication	**Brain Tumor (BT)**
Title	**Postoperative Seizure Prophylaxis in Meningioma Resection: A Systematic Review and Meta-Analysis**
Author	Batista et al.
Year	2023
Study Design	Systematic Literature Review and Meta-Analysis
Included Studies	9
Sample Characteristics Incl./Excl. Criteria	**Incl.:** studies with focus on seizure prophylaxis in surgically removed meningiomas **Excl.:** lacking data on seizure events, case reports, letters, comments, papers without clear information on reported meningioma tumors
Research questions	Regarding seizure occurrence is there any advantage of ASM use vs. no ASM in postoperative meningioma resection
Endpoints	Postoperative seizure frequency
Timing of intervention	Post meningioma resection
Duration of intervention	Early period up to 7 days post operatively Late stage > 7 days up to 12 months
Dosage of ASM	No specific information about dosage given
Quality assessment	Risk of bias in non-randomized studies of interventions (ROBINS-I)
Follow Up	Early period up to 7 days post operatively Late stage > 7 days up to 12 months
Conclusions	ASM post meningioma resection without seizures is not universally justified as seizure frequency could not be significantly reduced in patients receiving ASM
Recommendations	Cautious and individualized approach in assessing an ASM therapy for all patients, no significant reduction in seizure occurrence could be found, majority of seizures tend to happen within 7 days post-surgical intervention
Limitations	High heterogeneity among studies, random-effects models in all analyses. No sufficient evidence can be provided when talking about efficacy of prophylactic ASM use in postoperative meningioma resection use, LEV use just in 4 out of 9 studies, absence of comparative data in group of patients without ASM therefore no possibility to definitively establish a protective and potential effect of ASM during the early stage. No clear conclusion about potential protective effect of ASM regarding early stage in patients with new-onset seizure postoperatively can be drawn due to lack of comparative data in patients without ASM, no stratification is made among different ASM use, inclusion of studies is associated with intermediate level of quality, heterogeneity, lack of detailed information about ASM dosage impedes comparison of studies and true effectiveness of ASM, different follow up times impede a homogeneous comparison

Indication	**Neurocritical Care (NC)**
Title	**Levetiracetam for Seizure Prophylaxis in Neurocritical Care: A Systematic Review and Meta-Analysis**
Author	Fang et al.
Year	2022
Study Design	Systematic Review and Meta-Analysis
Included Studies	30
Sample Characteristics Incl./Excl. Criteria	**Incl.:** hospitalized Adults in neurocritical care (>18 years of age) with TBI, ICH, SAH, supratentorial neurosurgical interventions, studies using LEV as seizure prophylaxis, comparison with no ASM or other ASM-medications **Excl.:** patients with history of seizure, epilepsy, pediatric publications, case series, nonhuman studies, preclinical studies
Research questions	1.) LEV vs. no ASM 2.) LEV vs. other ASM as prophylaxis for preventing first seizure
Endpoints	prevention of first seizure
Timing of intervention	Prophylaxis after neurosurgical event or hospital admission
Duration of intervention	Heterogenous studies duration among intervention between 3-7 days, some used ASM for 6 weeks
Dosage of ASM	No clear recommendation 500 mg twice daily as most used dosage among included studies Generally, dosages ranged from 250-1500 mg twice daily
Quality assessment	RCT → Cochrane risk of bias 2 tool (Rob2) Nonrandomized studies → ROBINS-I Quality assessment was reviewed by a second author
Follow Up	Variety of follow-up periods, especially most of the included works were retrospective and follow-up durations differed within the comparator groups of the same study And less studies which evaluated periods exceeding 7 days
Conclusions	No benefit for the prophylactic LEV use in comparison to no ASM or other ASM was detected in pooled cohorts of patients with TBI, ICH, SAH or supratentorial neurosurgery Considering in subgroup meta-analyses for TBI, ICH or SAH similar findings as above mentioned were made Controversially, LEV significantly reduced seizure events in the supratentorial neurosurgery subgroup vs. patients who received PHT or VPA but compared with the group who did not receive ASM at all vs. LEV there was no significant difference in seizure events
Recommendations	1.) and 2.) no specific recommendation can be made, as the studies are heterogenous, and the meta-analysis did not demonstrate significant reduction in incident seizure. Neither support nor refute the use of LEV as prophylaxis in TBI, SAH, ICH or supratentorial neurosurgery can be made
Limitations	For the outcome as well early seizures (within 7 days) as late seizures were considered, included studies used low doses of LEV (250 mg-500 mg) and this may result in insufficient therapeutic levels, heterogenous data impedes giving a clear conclusion

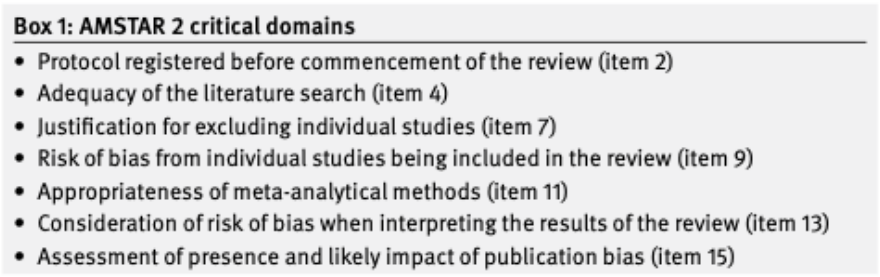
Indication	**Neurocritical Care (NC)**
Title	**Evidence-based recommendations for the prophylactic use of antiseizure medications (ASMs) in neurosurgery: a systematic review of guidelines**
Author	Jiang et al.
Year	2025
Study Design	Systematic Review
Included Studies	27
Sample Characteristics Incl./Excl. Criteria	**Incl.:** studies within the last 20 years, clinical practice guidelines, consensus and expert opinions developed and published by national or international organizations, guidelines related to the perioperative prophylactic use of antiseizure medications in neurosurgery including primary and secondary prophylaxis, Language: English and/or Chinese **Excl.:** not neurosurgical perioperatively prophylactic ASM related topics, Duplicates, non-updated versions or excerpts from guidelines, secondary evaluations, or interpretations of guidelines
Research questions	Evaluation of the methodological quality of guidelines and summary of all recommended aspects for both primary (in seizure naive patients) and secondary seizure (after experienced seizure) in neurosurgery
Endpoints	Methodological quality assessment of referred guidelines
Timing of intervention	No exact information about timing given, dependent on the respective key focus
Duration of intervention	No exact information about duration of intervention given, dependent on the respective key focus
Dosage of ASM	No exact information about dosage given
Quality assesment	Appraisal of guidelines for Research and Evaluation II (AGREE II), Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)
Follow Up	3-7days, 2 weeks, 3 months after surgery, 1-2 years after surgery
Conclusions	Guidelines recommend starting ASM after the first seizure as soon as possible but none of the guidelines specify the duration of prophylactic use as it lacks consensus- variability from 3 days to two years based on seizure incidence
Recommendations	In absence of seizures before and after surgery ASM use is recommended for a duration of 3 days to 2 weeks after seizure occurrence post-surgery ASM use for 3 months to one year. If preoperative seizure history continuation of ASM 1-2 years post-surgery. No ASM discontinuation for patients with glioblastoma and anaplastic gliomas with incomplete tumor resection or postoperative refractory epilepsy
Limitations	20 evidence-based guidelines, 6 expert consensus, 1 non-evidence-based guideline, moderate quality, dosage information insufficient

10.3 Data Collection Sheet

Variable	Einheit/Kategorie
Demografie/Komorbiditäten	
Patienten-ID (anonymisiert)	Zahl
Geburtsdatum	TT.MM.JJJJ
Alter	Zahl
Geschlecht	0=w_1=m
Aufnahmedatum	TT.MM.JJJJ
OP Datum	TT.MM.JJJJ
Art der Intervention	Freitext
Neurochirurgische Diagnose	Freitext
Neurochirurgische Diagnose wenn ICD Codierung vorhanden	ICD-Codierung
Chirurgische Reintervention während des Aufenthaltes notwendig	0=nein_1=ja
Levetiracetam Gabe	
Dokumentation des Anfalles im AKIM	0=nein_1=ja
Anzahl der dokumentierten Anfälle während des stationären Aufenthaltes	Zahl
Zeitpunkt der Verordnung prä OP	0=nein_1=ja
Zeitpunkt der Verordnung post OP	0=nein_1=ja
Dosierung	Zahl
Dosierungsintervall 2x täglich	0=nein_1=ja
Dosierungsintervall 1x täglich	0=nein_1=ja
Dosisänderung	0=nein_1=ja
Dosiserhöhung im Verlauf des stat. Aufenthaltes	0=nein_1=ja
Dosiserniedrigung im Verlauf des stat. Aufenthaltes	0=nein_1=ja
Angaben zur Therapiedauer (zeitl. Begrenzung Vermerk in Kurve oder Entlassungs-Brief)	0=nein_1=ja
Wenn zutreffend dann was für eine Art von Dokumentation und wo wurde diese geführt (bsp. nur im AKIM für die Interne Einsicht oder im Entlassungsbrief)	Freitext
Abweichung von den Empfehlungen aus der Literaturrecherche und Leitlinien	0=nein_1=ja
Kommentar zur Abweichung der Leitlinienkonformität	Freitext
Übereinstimmung mit den Guidelines und Empfehlungen der Gesellschaften	
Übereinstimmung mit den Guidelines	0=nein_1=ja

10.4 Critical AMSTAR-2 Domains and Overview of Included Studies from the Systematic Review

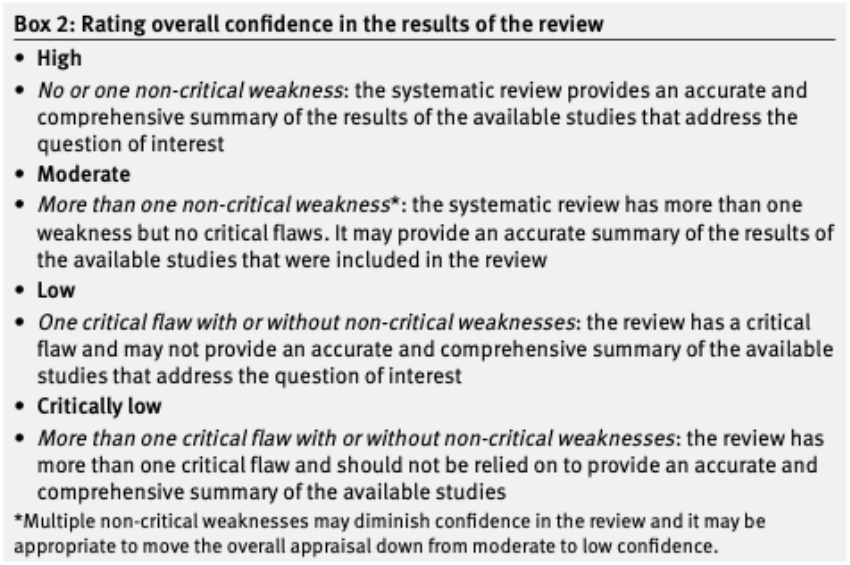
Moreover, AMSTAR-2 accounts critical domains which are presented in the following picture below. Based on the number of correspondences of critical items, the overall result is influenced.



Box 1: AMSTAR 2 critical domains

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)

Figure 7 Shea et al., 2017; AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Published in BMJ, 2017, p.5. Copy of Box 1.



Box 2: Rating overall confidence in the results of the review

- **High**
- *No or one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate**
- *More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low**
- *One critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low**
- *More than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Figure 8 Shea et al., 2017; AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Published in BMJ, 2017, p6. Copy of Box 2.

AMSTAR-2 criteria	**1. *Wilson et al,. 2018(53)***	**2. *Wat et al., 2019(54)***	**3. *Frontera et al., 2024(2)***	**4. *Won et al,. 2017(55)***	**5. *Gigliotti et al,. 2021(52)***	**6. Pourzitaki et al., 2016(56)**	**7. *Walbert et al. 2021(58)***	**8. *Batista et al,. 2023(57)***	**9. *Fang et al,. 2022(59)***	**10. *Jiang et al. 2025(60)***
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2*	N	N	N	PY	N	PY	N	PY	N	N
3	N	Y	Y	N	Y	Y	Y	Y	Y	Y
4*	PY	PY	PY	PY	PY	PY	PY	PY	PY	PY
5	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
6	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
7*	N	N	N	N	N	N	N	N	N	N
8	PY	PY	Y	PY	PY	Y	PY	Y	Y	PY
9*	PY	Y	Y	n.a.	n.a.	Y	N	n.a.	Y	N
9*	n.a.	PY	Y	N	PY	n.a.	N	Y	Y	n.a.
10	N	N	N	N	N	N	N	N	N	N
11*	Y	Y	Y	n.a.	n.a.	Y	N	n.a.	Y	N
11*	n.a.	Y	Y	N	Y	n.a.	N	N	N	n.a.
12	Y	Y	Y	N	N	Y	N	Y	Y	N
13*	N	Y	Y	N	Y	Y	N	Y	Y	Y
14	N	Y	Y	N	Y	Y	Y	Y	Y	Y
15*	N	Y	N	N	Y	N	N	N	Y	N
16	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results obtained from AMSTAR-2	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL

Table 13 Overview of AMSTAR-2 quality assessment results of the included systematic reviews
*Critical AMSTAR-2 items;CL= critically low
Y= Yes, PY= partially yes, N= No, n.a.= not applicable

1 PICO design
2 protocol
3 study selection
4 literature search strategy
5 study selection
6 data extraction
7 excluded study list
8 Search transparency
9 risk of bias assessment
10 funding sources among included studies
11 analysis methods
12 risk of bias assessment in individual studies
13 publication bias
14 heterogeneity
15 quality weighting
16 conflicts of inter

10.5 Ethics Committee Approval Letter

ethik kommission
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Votum:

EK Nr: 1152/2025
Projekttitel: Literaturübersicht und Arzneimittelverordnungsanalyse zu Levetiracetam-Verordnungen im perioperativen neurochirurgischen Umfeld
Antragsteller/in: Frau Karla-Nikita Singeorzan
Institution: Anstaltsapotheke Universitätsklinikum AKH Wien
Sponsor: Medizinische Universität Wien

Art des Projektes:

- **Retrospektive Datenauswertung**
- **Sonstiges**(z.B. Diätetik, Epidemiologie, etc.), bitte spezifizieren:
Medicine in Use Evaluation- Arzneimittelverordnungsanalyse
- **Masterarbeit**

Teilnehmende Prüfzentren:

Ethik-Kommission	Prüfzentrum	Prüfärztin/arzt
Ethikkommission der Medizinischen Universität Wien	Universitätsklinik für Neurochirurgie, AKH Wien	Herr Mag.pharm. Dr. Gunar Stemer MBA,MPH, aHPh

Die Stellungnahme der Ethik-Kommission erfolgt aufgrund folgender eingereichter Unterlagen:

Conflict of Interest

Name	Version	Datum
Conflict of interest_GS	--	07.02.2025

Lebenslauf (CV)

Name	Version	Datum
CV STEMER 112024	--	15.11.2024

Sonstige

Name	Version	Datum
Verpflichtungserklärung für Umgang mit Patientendaten_KS	--	07.02.2025
V03_Stemer_Singeorzan_1152_2025-submission-form-ek-5-20250424	--	24.04.2025

Studienprotokoll (Prüfplan)

Name	Version	Datum
Singeorzan_Projektplan_GS_final_V03	V03	24.04.2025

Die Kommission fasst folgenden Beschluss (mit X markiert):

X	Es besteht kein Einwand gegen die Durchführung der Studie. ACHTUNG: Unter Berücksichtigung der "ICH-Guideline for Good Clinical Practice" gilt dieser Beschluss ein Jahr ab Datum der Ausstellung. Gegebenenfalls hat der Antragsteller eine Verlängerung der Gültigkeit rechtzeitig zu beantragen.

Ergänzende Kommentare der Sitzung am 11.03.2025:

Zum Prüfplan:
Die statistische Analyse ist zu allgemein gehalten. Es sollte detailliert beschrieben werden, welche Fragestellung anhand welcher Variablen mit welchen statistischen Methoden (sowohl genaue Beschreibung, welche deskriptiven Kennzahlen für welche Variablen und Subgruppen berechnet werden sollen, als auch detaillierte Beschreibung der statistischen Hypothesentests und Regressionsmodelle) beantwortet werden soll.
Im Protokoll sollen insbesondere die Analyse für die primäre Fragestellung angegeben und die restlichen Analysen als sekundäre (explorative) Analysen spezifiziert werden.
Falls mehr als ein statistischer Test durchgeführt werden soll, ist das Problem multipler Hypothesentests (und eine mögliche Testkorrektur) zu diskutieren. Die Ethik-Kommission empfiehlt in diesem Zusammenhang die Unterteilung in EINE primäre Fragestellung (mit einem statistischen Test) und weitere sekundäre sowie exploratorische Fragestellungen.

Andere:
Das unterschriebene Antragsformular ist nachzureichen.

Die Ethik-Kommission ersucht die Antragsteller:innen, bei der Wiedervorlage von geänderten Unterlagen ein Exemplar mit hervorgehobenen Änderungen beizulegen.

Hinweis:
Die Ethikkommission verweist auf die allenfalls erforderliche Konsultation der Rechtsabteilung der MedUni Wien, der Datenclearingstelle der MedUni Wien, des:der Datenschutzbeauftragten der MedUni Wien bzw. des:der Datenschutzverantwortlichen des AKH sowie auch auf die

verpflichtend einzuhaltenden GSP Richtlinien der MedUni Wien und die Vorgaben des Handbuchs für Drittmittelprojekte der MedUni Wien.
Weitere Informationen finden sich unter https://ethikkommission.meduniwien.ac.at/service/weitere-informationen/

Ergänzende Kommentare:
Nachtrag vom 30. April 2025:
Die Antragsteller:innen legen am 24.04.2025 überarbeitete Unterlagen vor, die von der Ethik-Kommission akzeptiert werden. Das unterzeichnete Antragsformular wurde nachgereicht.

Hinweis:
Die Ethikkommission verweist auf die allenfalls erforderliche Konsultation der Rechtsabteilung der MedUni Wien, der Datenclearingstelle der MedUni Wien, des:der Datenschutzbeauftragten der MedUni Wien bzw. des:der Datenschutzverantwortlichen des AKH sowie auch auf die verpflichtend einzuhaltenden GSP Richtlinien der MedUni Wien und die Vorgaben des Handbuchs für Drittmittelprojekte der MedUni Wien.
Weitere Informationen finden sich unter https://ethikkommission.meduniwien.ac.at/service/weitere-informationen/

Die aktuelle Mitgliederliste der Ethik-Kommission ist unter folgender Adresse abrufbar:
http://ethikkommission.meduniwien.ac.at/ethik-kommission/mitglieder/

Mitglieder der Ethik-Kommission, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher laut Geschäftsordnung an der Entscheidungsfindung/Abstimmung nicht teilgenommen haben: **keine**

Dieses Dokument ist für berechtigte Benutzer/innen in digitaler Form unter folgender Adresse abrufbar:
https://ekmeduniwien.at/vote/32027/download/

10.6 Approved Study Project Plan

Projektplan

Literature review and drug prescription analysis of Levetiracetam prescriptions in the perioperative neurosurgical setting

Literaturübersicht und Arzneimittelverordnungsanalyse zu Levetiracetam-Verordnungen im perioperativen neurochirurgischen Umfeld

Version 3.0
Erstellt am 24.04.2025

Antragstellerin: Mag.pharm. Karla-Nikita Singeorzan
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Inhaltsverzeichnis

1 Hintergrund

Levetiracetam ist, v.a. aufgrund des günstigen pharmakodynamischen Profils aber auch wegen fehlendem Interaktionsprofil mit anderen Wirkstoffen, einer der am häufigst verordneten Wirkstoffe aus der Klasse der Antikonvulsiva. Dennoch sind auch für Levetiracetam Nebenwirkungen, wie z.B. Somnolenz, Kopfschmerzen, Depressionen, Aggressionen, Wesensveränderung u.v.m. dokumentiert. (Lyseng-Williamson et al., 2011; Celdran de Castro et al., 2023)

Im Rahmen diverser Erkrankungen, wie z.B. Schädel-Hirntraumata, intrazerebralen Blutungen, Subduralhämatomen oder auch bei Vorhandensein eines Hirntumors sind neurochirurgische Eingriffe oft unumgänglich. In der perioperativen Phase kann es vermehrt zu epileptischen Anfallsgeschehen kommen, auch wenn keine Epilepsie-Diagnose vorliegt. Das Risiko für Anfälle in der perioperativen Phase hängt von den jeweiligen pathophysiologischen Zuständen der Betroffenen ab und kann sich nach chirurgischer Intervention wieder ändern. (Hirschmann et al., 2021)

Die Datenlage, welche die Empfehlungen in Bezug auf Therapiestart mit Antikonvulsiva im neurochirugischen Kontext empfiehlt, ist heterogen und richtet sich primär nach Indikation des Eingriffes. Zudem wird auch individuell aus Sicht des Operateurs über eine patientenindividuelle antikonvulsive Therapie entschieden. Basierend auf diesem Wissen werden Levetiracetam Verordnungen zur Anfallsprophylaxe sowohl bei als auch ohne stattgefundenem epileptischen Anfallsgeschehen etabliert. (Frank et al., 2022; Pourzitaki et al., 2016; Peter-Derex et al., 2022)

Die Optimierung von Levetiracetam Neuverschreibungen, wie auch das Absetzen (Deprescribing) bei nicht vorhandener Indikation stellt eine wesentliche Maßnahme zur Erhöhung der Arzneimitteltherapiesicherheit in dieser Patient*innengruppe dar.

2 Ziel der Studie

Das Ziel der Studie ist sowohl den qualitativen als auch den quantitativen Einsatz von Levetiracetam Neuverordnungen im perioperativen neurochirurgischen Setting zu analysieren. Die daraus gewonnenen Erkenntnisse sollen zu einem optimierten Einsatz in den jeweiligen Indikationen beitragen, sodass nicht indizierte prolongierte Verordnungen vermieden werden können.

In einer systematischen Literaturrecherche in PubMed und EMBASE werden Empfehlungen zu einer Evidenz-basierten Levetiracetam-Verschreibung im perioperativen Kontext neurochirurgischer Patient*innen synthetisiert.

In einer nachfolgenden retrospektiven Arzneimittelverordnungsanalyse werden Levetiracetam-Verordnungen hinsichtlich Indikation, Dosierung und Verordnungsdauer in neurochirurgischen Patient*innen gegen die synthetisierten Evidenz-basierten Kriterien auditiert.

2.1 Primäre Forschungsfrage

Im perioperativen Kontext neurochirurgischer Patient*innen ohne Epilepsie- Anamnese, wie hoch ist der Übereinstimmungsgrad von Levetiracetam-Neuverordnungen mit Evidenz-basierten Kriterien zur Prophylaxe eines Anfallsgeschehens, in Hinblick auf Indikationsstellung, Dosierung und Dauer?

2.2 Sekundäre Forschungsfrage

Im perioperativen Kontext neurochirurgischer Patient*innen ohne Epilepsie- Anamnese, wie hoch ist der Übereinstimmungsgrad von Levetiracetam-Neuverordnungen mit Evidenz-basierten Kriterien zur Therapie eines Anfallsgeschehens, in Hinblick auf Indikationsstellung, Dosierung und Dauer?

2.3 Bedeutung der Studie

Die Ergebnisse der Verordnungsanalyse können dazu dienen, das Potenzial aufzuzeigen, Levetiracetam-Verordnungen im perioperativen neurochirurgischen Setting zu optimieren und einen Evidenz-basierten Einsatz zu fördern.

3 Studiendesign

Retrospektiv deskriptive Datenerhebung über eine Dauer von 6 Monaten (Mai-Oktober 2024) in Patient*innen ≥18 Jahre, die aufgrund einer chirurgischen Intervention im Rahmen eines stationären Aufenthaltes auf der Abteilung für Neurochirurgie am Universitätsklinikum AKH Wien versorgt worden sind.

3.1 Studienpopulation

- **Einschlusskriterien:**
  - Patient*innen ≥18 Jahre
  - Stationäre Aufnahme und operative Versorgung an der klinischen Abteilung für Neurochirurgie des Universitätsklinikums AKH Wien
  - Neuverordnung von Levetiracetam während des stationären Aufenthaltes, unabhängig von Dosierung und Applikationsart

- **Ausschlusskriterien:**
  - Patient*innen mit einer Diagnose Epilepsie zum Zeitpunkt der stationären Aufnahme
  - Patient*innen mit der Diagnosestellung Epilepsie während des stationären Aufenthaltes
  - Patient*innen die schon ein Levetiracetam in der Dauermedikation hatten, vor dem Zeitpunkt der stationären Aufnahme

4 Methodik

4.1 Datensammlung

Alle Patient*innen die im definierten Zeitraum von 6 Monaten (Mai-Oktober 2024) auf der Abteilung für Neurochirurgie am Universitätsklinikum AKH Wien im Rahmen des stationären Aufenthaltes behandelt worden sind und wo eine Therapie mit Levetiracetam neu etabliert worden ist, werden mit Hilfe des Krankenhausinformationssystems (AKIM) identifiziert, sofern sie den restlichen Studieneinschlusskriterien entsprechen. (siehe 3.1 Studienpopulation) Die Einsicht in die Patientenakte, einschließlich Eingriff, Medikation bei der Aufnahme als auch die Medikation bei der Entlassung ist dadurch ersichtlich und erhebbar. Die Datensammlung erfolgt im Rahmen der schon klinisch pharmazeutisch betreuten Patienten, welche routinemäßig klinisch pharmazeutisch auf der Abteilung für Neurochirurgie betreut werden.

4.2 Parameter

Folgende Variablen werden erhoben und in Form einer Excel-Datei fortlaufend dokumentiert.

Variable	Einheit/Kategorie
Demografie/Komorbiditäten	
Patienten-ID (anonymisiert)	Zahl
Geburtsdatum	TT.MM.JJJJ
Alter	Zahl
Geschlecht	0=w_1=m
Aufnahmedatum	TT.MM.JJJJ
OP Datum	TT.MM.JJJJ
Art der Intervention	Freitext
Neurochirurgische Diagnose	Freitext
Neurochirurgische Diagnose wenn ICD Codierung vorhanden	ICD-Codierung
Chirurgische Reintervention während des Aufenthaltes notwendig	0=nein_1=ja
Levetiracetam Gabe	
Dokumentation des Anfalles im AKIM	0=nein_1=ja
Anzahl der dokumentierten Anfälle während des stationären Aufenthaltes	Zahl
Zeitpunkt der Verordnung prä OP	0=nein_1=ja
Zeitpunkt der Verordnung post OP	0=nein_1=ja
Dosierung	Zahl
Dosierungsintervall 2x täglich	0=nein_1=ja
Dosierungsintervall 1x täglich	0=nein_1=ja
Dosisänderung	0=nein_1=ja
Dosiserhöhung im Verlauf des stat. Aufenthaltes	0=nein_1=ja
Dosiserniedrigung im Verlauf des stat. Aufenthaltes	0=nein_1=ja
Angaben zur Therapiedauer (zeitl. Begrenzung Vermerk in Kurve oder Entlassungs-Brief)	0=nein_1=ja
Wenn zutreffend dann was für eine Art von Dokumentation und wo wurde diese geführt (bsp. nur	Freitext

im AKIM für die Interne Einsicht oder im Entlassungsbrief)	
Abweichung von den Empfehlungen aus der Literaturrecherche und Leitlinien	0=nein_1=ja
Kommentar zur Abweichung der Leitlinienkonformität	Freitext
Übereinstimmung mit den Guidelines und Empfehlungen der Gesellschaften	
Übereinstimmung mit den Guidelines	0=nein_1=ja

Tabelle 1 Datenerhebungsblatt

4.3 Hauptzielparameter (Primärer Zielparameter)

Untersuchung von Levetiracetam Neuverordnungen im neurochirurgischen Umfeld hinsichtlich Übereinstimmung mit Leitlinien und den Empfehlungen bzw. Konformität mit evidenzbasierter Studienlage

Nach vorangegangener Literaturrecherche sollen die Ergebnisse um Empfehlungen aus den entsprechenden Leitlinien ergänzt werden und Optimierungsmaßnahmen hinsichtlich Indikationsstellung, Dosierung und Dauer gestellt werden.
Die vorliegende Analyse soll die Leitlinienkonformität sowie die evidenzbasierte Studienlage zur Levetiracetam Neuverordnung im perioperativen neurochirurgischen Setting zur Anfallsprophylaxe, bei nicht stattgehabtem Anfallsgeschehen im erwähnten Patient*innen-Kollektiv, beleuchten.

Es sollen vor allem Indikationsstellung, Dosierung und Dauer der Levetiracetam Verordnungen untersucht werden. Die Findung von evidenzbasierten Kriterien, die den Einsatz bewerten, sollen herangezogen werden. Durch diese Erkenntnisse soll eine Optimierung des Einsatzes, hinsichtlich Indikationsstellung, Dosierung und Dauer, angestrebt werden. Dies soll zum einen, die nicht zwingende prolongierte Therapie umgehen, als auch Sicherheitsaspekte der Patienten miteinbeziehen, v.a. in Hinblick auf mögliche Nebenwirkungen wie Depressionen, Wesensveränderungen etc.. Diese könnten mit einer gezielten und zeitlich begrenzten Verordnung im Sinne der Arzneimitteltherapiesicherheit optimiert werden. (Celdran de Castro et. al 2023)

4.4 Sekundäre Zielparameter

Die Analyse der Leitlinienkonformität, welche durch die evidenzbasierte Studienlage erweitert wird, soll den Einsatz von Levetiracetam Neuverordnungen im perioperativen neurochirurgischen Umfeld bei stattgehabten Anfallsgeschehen, zur Anfallstherapie, verdeutlichen. Kriterien welche die Indikationsstellung, Dosierung und Dauer der Levetiracetam Neuverordnung aufzeigen, sollen gefunden werden, um den evidenzbasierten gezielten Einsatz zu veranschaulichen.

Durch das Aufzeigen eines fokussierten Einsatzes von Levetiracetam Neuverordnungen könnten in diesem Setting durch genauere Dokumentation und Vermerke Bsp. im Entlassungsbrief die Schnittstelle zur Weiterversorgung im niedergelassenen Bereich optimiert werden. Allenfalls würde hier das Potenzial bestehen Dauerverschreibungen ohne Diagnose Epilepsie zu umgehen.

5 Datenanalyse

Statistische Analyse:
Die Analyse der demographischen und klinischen Daten zur Darstellung der Patient*innen-Population erfolgt mittels deskriptiver, statistischer Kennwerte, wie z.B. Mittelwerte, Standardabweichung, Median und Interquartilabständen.

Der primäre Endpunkt ‚Übereinstimmungsgrad der Levetiracetam-Neuverordnungen im Kontext zur Anfallsprophylaxe' wird als Prozentanteil der mit Evidenz-basierten Kriterien übereinstimmenden Verordnungen an allen, im Datenerhebungszeitraum erfolgten Levetiracetam-Verordnungen zur Anfallsprophylaxe berechnet (Kategoriale Variable Leitlinienkonformität, Subgruppe Variable Anzahl an dokumentierten Anfällen = 0). Dieser Prozentanteil wird einerseits als Gesamtwert und für die Domänen Dosierung und Dauer gesondert dargestellt.

Ein potenzieller Einfluss ausgewählter Variablen (z.B. Alter, neurochirurgische Diagnose) auf die kategoriale Variable Leitlinienkonformität/Anfallsprophylaxe wird im Rahmen einer logistischen Regressionsanalyse erhoben.

Der sekundäre Endpunkt ‚Übereinstimmungsgrad der Levetiracetam-Neuverordnungen im Kontext der Anfallstherapie' wird als Prozentanteil der mit Evidenz-basierten Kriterien übereinstimmenden Verordnungen an allen, im Datenerhebungszeitraum erfolgten Levetiracetam-Verordnungen zur Anfallstherapie berechnet (Kategoriale Variable Leitlinienkonformität, Subgruppe Variable Anzahl dokumentierter Anfälle = Zahl). Dieser Prozentanteil wird einerseits als Gesamtwert und für die Domänen Dosierung und Dauer gesondert dargestellt.

Ein potenzieller Einfluss ausgewählter Variablen (z.B. Alter, neurochirurgische Diagnose) auf die kategoriale Variable Leitlinienkonformität/Anfallstherapie wird im Rahmen einer logistischen Regressionsanalyse erhoben.
Für die Analyse der erhobenen Daten wird die Software IBM SPSS® Statistics Version 29.0 verwendet.

6 Datenschutz

Zur Durchführung des Projektes sind sämtliche personenbezogene Daten aller in dieser Studie eingeschlossener Patient*innen erforderlich. Diese Daten, welche im Rahmen des Projektes erhoben werden, wie z.B. medizinische Befunde, Anamnesen, Behandlungsarten, Medikamente aus der Dauerverordnung, im perioperativen Setting neu angesetzte Wirkstoffe, inklusive sonstiger personenbezogener Informationen welche zur optimalen Dokumentation und Datenerhebung dieses Projektes beitragen, werden nur in pseudonymisierter Form geführt. Somit besteht kein direkter Bezug zum Patient*innen-Namen. Dies wird durch den Vermerk der Fallzahl (numerisch) und konkominant geführter laufender Nummer in einem Excel Dokument vermerkt. Das Dokument wird auf einem PC mit Zugriffsbeschränkung abgespeichert, lokalisiert in der Anstaltsapotheke AKH Wien, Abteilung für Arzneimittelinformation und klinische Pharmazie. Zugang zum dem PC haben nur autorisierte Personen. Eine Verpflichtung zur Kenntnisnahme und Einhaltung des Datenschutzes, gemäß DSGVO, liegt im Rahmen der beruflichen Tätigkeit im Universitätklinikum AKH Wien vor. Zudem wird eine unterzeichnete Verpflichtungserklärung für den Umgang mit Patientendaten dem Ethikantrag beigelegt.

7 Nutzen Risiko Evaluierung

Da es sich um eine retrospektive Datenerhebung handelt, folgt für die inkludierten Studienteilnehmer*innen kein direkter Nutzen von der Studie. Allerdings könnten durch die Datenerhebung und -auswertung wertvolle Erkenntnisse gewonnen werden, welche den Einsatz von Levetiracetam im perioperativen neurochirurgischen Setting optimieren könnten. Darüber hinaus würde der Benefit einer gezielten und zeitlich optimierten Verordnung nicht nur intramural von Vorteil sein, sondern auch extramural, wenn es zur Folge- bzw. Dauerverordnung kommt. Somit könnte eine nicht notwendige bzw. keine durch aktuelle Studienlage mit Nutzen belegte prolongierte Folgeverordnung bzw. Dauerverordnung umgangen werden. Des Weiteren ist anzumerken, dass keine der eingeschlossenen Personen einem physischen Risiko durch die retrospektive Studie ausgesetzt sind. Dies ist dem Studiendesign zuzuschreiben, welches den Fokus ausschließlich auf die Erfassung von Daten legt und nicht auf physische Eingriffe. Das einzig mögliche Risiko, das Bekanntwerden sensibler Daten, wird durch eine Pseudonymisierung und Zugriffsbeschränkung minimiert.

8 Literatur

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