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[Intervention Protocol]

Antiseizure medications for preventing a first seizure in adults with a brain tumour

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and tolerability of antiseizure medications (ASMs) in preventing a first seizure in people with brain tumours compared with placebo or no active treatment.

BACKGROUND

Description of the condition

The use of antiseizure medications for the prevention of a first seizure in adults with brain tumours varies, being common clinical practice in the USA (Joiner 2019), but less common in the UK (Jenkinson 2019). Evidence for their use is limited. It has been estimated that seizures are the presenting symptom in 15% to 30% of people diagnosed with a brain tumour, but this can go up to 75% in some tumour types (Recht 1997; Wieshmann 2015). Furthermore, up to 60% of people with a brain tumour experience a seizure at some point during their illness (Chen 2018; Ertürk Çetin 2017).

A seizure can be classified as having a focal onset, in which it originates from one hemisphere of the brain, or generalised if it originates simultaneously in both hemispheres. Focal onset seizures may evolve into bilateral tonic-clonic seizures (previously known as generalised tonic-clonic seizures) (Fisher 2017). Typically, brain tumour-associated seizures have a focal onset and may or may not evolve into a bilateral tonic-clonic seizure (Chen 2018; Ertürk Çetin 2017). Epilepsy is defined as: two or more unprovoked seizures occurring more than 24 hours apart; the specific diagnosis of an epilepsy syndrome; or a single unprovoked seizure if the recurrence risk is greater than 60% over the next 10 years (Mbizvo 2020). Antiseizure medications are indicated for those with a diagnosis of epilepsy. However, it remains unclear whether they are beneficial in preventing a first seizure in people with brain tumours (Tremont-Lukats 2008).

Diffuse glioma of lower grades (less aggressive) appears to be more strongly associated with seizures than gliomas of higher grades (more aggressive; World Health Organization (WHO) Grade 3 to 4) (Chang 2008; Chen 2018; Ertürk Çetin 2017). This finding may be explained by the longer life expectancy of people with low-grade tumours compared with high grades, and thus an increased likelihood of further seizures during their lifetime. Other potential contributing factors include a more gradual local tissue reorganisation allowing the formation of a functional seizure focus, and intrinsic functional properties of certain tumour types (Chen 2018; Ertürk Çetin 2017). The seizure risk of brain metastases may also relate to histological type, with metastatic melanoma having a higher risk of developing seizures than other histological types (Lamba 2021). The seizure risk of primary and secondary central nervous system (CNS) lymphoma appears to relate to underlying patient immunodeficiency (Aboubakr 2023; Fox 2019). While meningiomas commonly present with seizures, it is not clear that their histological subtype and grade influence seizure risk (Chen 2017; Chen 2018; Lieu 2000).

In addition to tumour histology, the location of the tumour in the brain also appears to be a significant contributing factor in epileptogenesis. Tumours in the frontal, temporal and parietal lobes appear to be more epileptogenic than occipital lobe tumours (Chang 2008; Liigant 2001; Pallud 2014). People with cortical tumours at the surface of the brain also appear to be more prone to seizures than those with deeper, subcortical tumours (Chang 2008; Pallud 2014). It has been suggested that location and proximity to the cortical grey matter are important factors in the development of epilepsy in people with diffuse glioma (You 2012). Furthermore, tumours in specific brain areas are associated with characteristic seizure types and seizure risk (Chang 2008; Lee 2010; Wang 2015).

The pathophysiology of seizures in brain tumours is poorly understood, with multiple mechanisms proposed. The possible mechanisms include mechanical compression, imbalance of vascularisation and oxygen demand of the tumour, inflammatory processes, and neurotransmitter imbalances (Seidel 2022). Of note, neurotransmitter imbalances lead to epileptogenicity of the tumour itself as well as of the tissue adjacent to the lesion, which means that the “epileptogenic zone” includes the peritumoral tissue (Seidel 2022). Therefore, even a complete resection of a brain tumour does not necessarily preclude an epileptogenic zone remaining. Mechanical compression may induce ischaemia and metabolic changes with subsequent blood brain barrier disruption leading to a higher risk of seizures (Seidel 2022). In recent years, we have developed an understanding of the connections between diffuse gliomas in particular and surrounding neurons – the field of so-called cancer neuroscience. The abnormal growth of tumour tissue likely results in the formation of a seizure focus (Chen 2018; Ertürk Çetin 2017), but seizure risk is related to both tumour pathophysiology and the effects of treatment, including surgery and radiotherapy. Diffuse gliomas are characterised by networks of interconnected brain tissue that form functioning synapses with surrounding brain tissue, and may collaborate with the surrounding tissue to drive tumour growth (Hausmann 2023; Venkataramani 2019). Other contributing factors are tumour histology, tumour genetics, tumour location within the brain, and vascular changes in the tumour microenvironment (Ertürk Çetin 2017; You 2012). After surgery, it is thought that localised reduced blood flow, bleeding and swelling increase the risk of seizures (Wirsching 2016).

Description of the intervention

Surgical resection can improve seizure control in people with brain tumours and is a positive predictor of survival (Chang 2008; Sanai 2008; Xu 2018). Seizure foci in diffuse gliomas are believed to reside within the tumour mass (Gilmore 1994). Seizure freedom after tumour resection or debulking occurs in up to two-thirds of people with meningiomas and low-grade gliomas (Englot 2014; Englot 2016), and is even higher in people with glioneuronal tumours (Englot 2014). Some people, however, continue to experience seizures after surgical intervention. Additionally, some people with brain tumours are not suitable candidates for surgical intervention. For such people, antiseizure medications (ASMs) form the mainstay of first seizure prevention.

There are three generations of ASMs (Perucca 2019). The first-generation ASMs are older but effective drugs that are still in routine clinical use. They include phenytoin, phenobarbital, sodium valproate and carbamazepine. Phenytoin, phenobarbital, and sodium valproate have a broad spectrum, including for emergency use, because of their availability as intravenous (IV) preparations, making them potentially suitable in surgical emergencies and status epilepticus. Oral valproate tends to be used in generalised epilepsy. Carbamazepine is an oral preparation that is often used for focal epilepsy. Newer second-generation ASMs were introduced in the late 1990s to early 2000s. They include lamotrigine, topiramate, oxcarbazepine, levetiracetam, and zonisamide (Mbizvo 2020). The most commonly used are lamotrigine and levetiracetam; the former for focal epilepsies, and the latter for either focal or generalised epilepsies. Levetiracetam is also effective in status epilepticus owing to its availability as an IV preparation. The second-generation ASMs are generally non-

inferior to the first-generation drugs in terms of their efficacy for treating seizures, and they are more popular in clinical practice owing to their improved safety and tolerability profiles (Perucca 2019). There is emerging evidence to support sodium valproate in generalised epilepsy and lamotrigine in focal epilepsy as perhaps the most effective options. Since 2010, a third generation of ASMs has been introduced, and these include levetiracetam's newer selective analogue brivaracetam, and others such as eslicarbazepine, perampanel, and vigabatrin (Mbizvo 2020). There are several potential indications for the use of ASMs in brain tumours: 1) prevention of seizure recurrence in those who have already experienced a first seizure, and 2) prophylactic prevention of first seizure either before or after surgery.

This review addresses the use of ASMs in the prevention of a first seizure in primary (originating from within the brain or its meninges) and secondary (metastasising from outside the brain) tumours, with or without surgical intervention.

How the intervention might work

Brain tumours cause focal seizures, where seizures initiate at a particular focus and either remain as a focal seizure or evolve into a bilateral tonic-clonic seizure (Chen 2018; Ertürk Çetin 2017). As such, ASM selection is generally tailored toward those most effective for focal epilepsies. The SANAD II trial results indicate that lamotrigine should remain a first-line treatment for people with focal epilepsy (Marson 2021). However, it remains unclear whether there is any role for ASMs in prophylaxis of a first seizure in people with brain tumours, and, if so, which drugs would be most effective (Marson 2021). Most ASMs work to alter voltage-gated sodium, calcium or potassium channels or on GABA receptors. It is hypothesised that, similar to their mechanism in focal epilepsy, these drugs can alter the neurotransmitter homeostasis at the seizure focus in brain tumours and reduce the likelihood of a seizure (Chen 2018; Ertürk Çetin 2017). There remains little evidence about the efficacy of different ASMs in brain-tumour-associated epilepsy. Additionally, ASMs are not without side effects, which can be severe and life-threatening (Schiff 2015). There is also the potential for ASMs to interact with other medical treatments for brain tumours, such as chemotherapeutic agents and steroids (Zaccara 2014). This can result in under-dosing of steroids and chemotherapeutic agents and therefore suboptimal tumour treatment. Additionally, there is the possibility of over- or under-dosing of ASMs, increasing toxicity and seizure risk, respectively (Zaccara 2014).

Why it is important to do this review

Evidence about the efficacy and tolerability of ASMs in people with brain tumours is limited, with heterogeneity between trials. In 2000, the American Academy of Neurology published a meta-analysis of four randomised controlled trials and recommended that prophylactic antiseizure medications should not be used routinely in people with newly diagnosed brain tumours (Glantz 2000). The four included studies differed substantially in design, however, and no test of heterogeneity was performed. A further meta-analysis also demonstrated a lack of efficacy of prophylactic ASMs in people with brain tumours with no history of seizures; however, phenobarbital, phenytoin and valproic acid were the only ASMs subject to analysis (Sirven 2004). A systematic review in 2008 also found no clear benefit of first seizure prevention in people with brain tumours, but noted substantial heterogeneity between trials (Tremont-Lukats 2008). Recent systematic reviews focused specifically on postoperative first seizure prevention in people who underwent craniotomy for meningioma (Englot 2016; Islim 2017), or all indications (Greenhalgh 2020), and concluded that there was insufficient evidence to advise the use of ASMs for these patients. Another systematic review investigated perioperative ASM use in people undergoing brain tumour resection with no prior seizure history, and suggested that ASM treatment may not be effective in the prevention of first seizure for this patient group (Chandra 2017). Evidence in people with brain metastases is also lacking (Mikkelsen 2010). Given the high prevalence of seizures in brain tumours and the high treatment burden of ASMs, there is an unmet need for an up-to-date systematic review and meta-analysis of all the available evidence from randomised controlled trials. To date, there is no evidence about which ASM is more efficacious in preventing a first seizure in adults with a brain tumour; therefore, a systematic review should consider all ASMs. This systematic review is intended as an update to the Cochrane review by Tremont-Lukats and colleagues (Tremont-Lukats 2008), to include more recent trials of second-generation ASMs for the prevention of first seizure in all types of brain tumours, both preoperatively and postoperatively.

OBJECTIVES

To assess the efficacy and tolerability of antiseizure medications (ASMs) in preventing a first seizure in people with brain tumours compared with placebo or no active treatment.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review, studies must meet the following criteria.

1. Randomised control trials (RCTs). We will consider parallel studies, cluster-randomised studies and cross-over studies (we intend to use data from the first phase of the study only).
2. Studies may be single-blinded, double-blinded or unblinded.
3. Control arm with placebo or no treatment.

We will search for trials in all languages and arrange translation of trial reports published in languages other than English.

Types of participants

Eligible participants will be adults (aged 18 years and above) with no previous history of seizures who have a histological or radiological diagnosis of a brain tumour.

We will use the following definitions of brain tumour.

- Supratentorial tumours
  - Diffusely infiltrative high-grade primary brain tumours (WHO Grade 3 to 4 gliomas, including CNS lymphoma)
  - Diffusely infiltrative low-grade primary brain tumours (WHO Grade 1 to 2 gliomas)
  - Non-diffusely infiltrative low-grade primary brain tumours (including pilocytic astrocytomas, glioneuronal tumours, ependymal tumours, embryonal tumours, and pineal tumours)
  - Cerebral metastases
  - Meningioma

- Infratentorial tumours and pituitary adenomas

We will include those with or without neurosurgical intervention in relation to the brain tumour.

For studies that only include a subset of relevant participants, we will contact the original study authors to request the data for the relevant subsets. We will make contact twice within a month and, if there is no response, list the study as 'awaiting classification'.

Types of interventions

We will include studies that compare ASMs (individual ASM given in monotherapy) versus control treatment (placebo or no treatment) for prevention of a first seizure.

Studies comparing one or more ASMs to each other with no control arm will not be eligible. We will not limit the search strategy by restricting the inclusion of studies based on a predefined list of ASMs, as this could miss newer drug treatments, but rather accept any studies using commonly accepted ASMs. These might include, for example, acetazolamide, adrenocorticotropic hormone (including tetracosactide), carbamazepine, clobazam, clonazepam, diazepam, eslicarbazepine, ethosuximide, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, eventrate, lorazepam, mepenzolate bromide, methsuximide, midazolam, nitrazepam, oxcarbazepine, perampanel, phenobarbital, phenytoin, piracetam, pregabalin, primidone, retigabine, rufinamide, sodium valproate, steripentol, sultiame, temazepam, tiagabine, topiramate, vigabatrin, and zonisamide.

We shall consider all medications at all doses.

The treatment groups will be people administered ASMs versus those on placebo or no treatment. We will group studies together regardless of length of follow-up in the primary analysis to help increase power if we find few studies. However, we will undertake a subgroup analysis, where possible, with studies subdivided by ASM medication type and follow-up time to help interrogate possible sources of heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Types of outcome measures

Studies should investigate the number of participants in a treatment group experiencing a first seizure (Primary outcomes) for inclusion, to ensure relevance to the review objectives. Given the variable duration of studies, we will consider any time points, but will group these into short term (< 30 days) and long term (> 30 days).

Primary outcomes

The primary outcome is the number of participants in a treatment group experiencing a first seizure within the study period, as a proportion of the total number of participants in that treatment group.

Secondary outcomes

1. Adverse events (as reported in the included studies) at any time after the introduction of treatment:
   a. the proportion of participants experiencing one or more adverse events in relation to ASM therapy;
   b. where possible, we will include additional information on whether any were graded as serious adverse events and by what criteria.
2. Health-related quality of life (QoL) scales
3. Proportion of participants who died within the study period

Search methods for identification of studies

Electronic searches

We will search the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (Ovid), using the search strategy shown in Appendix 1
- Embase (Ovid)

We will search all databases from their inception to current date, without language restrictions.

Additionally, we will search the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int) to ensure that we capture trials not yet on the CENTRAL database.

Searching other resources

To identify further references, we will review the reference lists of all included primary studies. Where required, we will contact experts in the field for information on any ongoing or unpublished trial data.

Data collection and analysis

Selection of studies

Two review authors (MAM and AB) will independently screen the titles and abstracts of all articles identified in the search to select potentially relevant studies for inclusion. They will retrieve the full-text articles for potentially relevant studies. The two review authors (MAM and AB) will then review the full texts and record the reasons for articles excluded at this stage. Any disagreements will be resolved by discussion, or by consensus with a third review author if required (GM). The review authors will identify and exclude any duplicate articles, and collate multiple reports from the same trial, to enable an overview of the true number of studies included, rather than the number of reports.

Review authors will record the selection process in detail, including reasons for the exclusion of articles, and produce a PRISMA flow diagram to describe the selection process (PRISMA 2020).

Data extraction and management

We will create a data collection database and use it to collect the following participant and study characteristics from the included trials.

1. Methods: trial design, trial location, setting and number of study centres, risk of bias domains, date of study.
2. Participants: number of people randomised in each intervention group and the number of people analysed, with reasons for any exclusions. We will also collect data on age, sex, type of brain tumour, performance status, preoperative or postoperative status, inclusion criteria and exclusion criteria.

3. Interventions: type of intervention and comparator, including combination interventions, method of intervention administration, any changes to interventions during the study.
4. Outcomes: primary and secondary outcomes as prespecified (see Types of outcome measures), time points of outcome assessment.
5. Additional: trial funding, study sponsors and author conflicts of interest.

If the information is not available in the published manuscript, we will contact the original investigators for further data.

Two review authors (MAM and AB) will independently extract outcome data from included studies and any disagreement will be resolved by discussion or consensus with the third review author if required (GM).

Assessment of risk of bias in included studies

Two review authors (MAM and AB) will independently assess the risk of bias in each included study using the Cochrane risk of bias tool RoB 1, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be resolved by discussion or consensus with a third author (GM).

There are seven parameters that the Cochrane RoB 1 tool examines.

1. Random sequence allocation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessors
5. Incomplete outcome data
6. Selective outcome reporting
7. Other biases.

We will assess bias for each of the domains as 'low', 'high', or 'unclear', according to the *Cochrane Handbook* (Higgins 2011).

Measures of treatment effect

Primary analysis will be on an intention-to-treat basis.

For dichotomous outcomes (including the primary outcome and adverse events), the preferred measure of treatment effect will be the Mantel-Haenszel risk ratio (RR) with 95% confidence intervals (CI) (99% CI for adverse events to allow multiple testing).

For continuous variables (e.g. changes in QoL scores over time), we will analyse the data as a mean difference along with 95% CIs. We are aware, however, that there are several different QoL measures that can be used for people with epilepsy, none of which have been validated specifically in this patient group. Additionally, QoL measures used in neuro-oncology have not been validated for use in a cohort of people with epilepsy. Therefore, the QoL scales represent two distinct disease processes and encapsulate a range of QoL measures. Where possible, we will combine results of studies that use the same QoL scale/measure. If this is not possible, we will summarise data in tables where individual studies report different scales.

Unit of analysis issues

The unit of analysis for the review will be the individual randomised participant.

For trials with multiple intervention arms (i.e. comparing more than one ASM), we will pool all ASMs in a single meta-analysis ('lumping'), within which we will explore specific characteristics as effect modifiers in subgroups focusing on different ASMs, as highlighted in the Methods; Subgroup analysis and investigation of heterogeneity section. Pooling all ASMs will address an important clinical question that remains unanswered about whether ASMs in general, regardless of the specific ASM used, have any effect on preventing a first seizure in people with brain tumours. For trials that use different doses of ASMs, we will pool the dose intervention arms using the methods described in the *Cochrane Handbook* (Higgins 2022).

If we identify any cross-over trials, we intend to use the data from the first phase of the study only. If we identify and include any cluster-randomised trials, we will include analysis methods to account for clustering in the data as specified in the *Cochrane Handbook* (Higgins 2022).

We will describe adverse events in a results table, giving the number of participants experiencing each individual side effect as a proportion of the total population of the study. We will report additional information about the severity of adverse events narratively within the text.

For outcomes that are assessed at several time points, we will consider the latest follow-up time point reported in each study for inclusion in the analysis.

Dealing with missing data

Where data are missing in a study article, we will contact study investigators or sponsors to confirm missing data, where possible. This may include participant characteristics, study design or outcomes. If it is not possible to obtain this information, we will perform sensitivity analyses to assess the impact of this missing data on the validity of the overall results.

Assessment of heterogeneity

For each analysis, we will use the I^2 statistic and Chi^2 test to quantify statistical heterogeneity between the trials. We will assess the included studies for clinical diversity by considering differences in the participants, setting, interventions and outcomes assessed. If substantial clinical heterogeneity is identified (Higgins 2022), we will report it as such and investigate potential causes of the heterogeneity using the formal test for subgroup interactions in Review Manager (RevMan 2025). In our consideration of clinical heterogeneity, we will use the categories described in Subgroup analysis and investigation of heterogeneity. We will also consider whether there are methodological differences in the study design, or risk of bias. Diversity in these factors will impact the validity of pooling data from different studies, which we will comment on during our overall synthesis. However, an important clinical question remains about whether ASMs as a group, regardless of the specific ASM chosen, have any impact on preventing a first seizure in people with brain tumours, necessitating an empirical pooled comparison. We may consider the sources of heterogeneity when assessing outcomes using the GRADE approach.

Assessment of reporting biases

If we include a sufficient number of studies (10 or more) for an outcome measure, we will create a funnel plot to assess

reporting bias, inspecting it visually to assess for bias. If there is observed asymmetry of the funnel plot, we will formally assess the asymmetry using Egger's test (Egger 1997; Sterne 2011). If there are fewer than 10 studies, it will not be possible to assess reporting bias.

Data synthesis

We will summarise data using the standard methodologies as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

In order to assess clinical heterogeneity among the included studies, we will compare their characteristics, then quantify the heterogeneity statistically using the I^2 statistic and Chi^2 test (see Assessment of heterogeneity).

If we deem the studies to be clinically homogenous, we will analyse the data for the studies using a fixed-effect model. If we deem substantial clinical heterogeneity in study and participant characteristics to be present, we will use a random-effects model. A random-effects model may also be used as a sensitivity analysis where studies and outcome data are deemed to be clinically homogenous, yet high levels of statistical heterogeneity are present, according to the I^2 statistic.

Our primary analysis (main comparison) will be ASMs versus placebo or no active treatment. We will pool the data from individual ASMs (all subtypes lumped together) in a single meta-analysis to create a pairwise comparison of ASMs versus placebo or no treatment.

Where a random-effects model is used, we will undertake subgroup analyses to investigate potential causes of heterogeneity (see Subgroup analysis and investigation of heterogeneity).

A subgroup analysis of our primary and secondary outcomes will compare the results of individual ASMs to placebo or no treatment. We will assess ASMs versus control as separate comparisons, and present these as separate subgroup analyses in RevMan.

Subgroup analysis and investigation of heterogeneity

We will undertake a subgroup analysis of the primary and secondary outcomes. We will separate participants according to the following groups of interest due to their distinct aetiologies, prognosis, reported seizure risk in the literature, or typical management relevant to the efficacy and safety of anticonvulsant treatment (Li 2022; Louis 2021). Surgical intervention may increase or decrease seizure risk, depending on immediacy postoperatively and surgical intervention performed.

1. ASM monotherapy stratified by medication type

We will compare individual ASMs to placebo or no treatment.

2. Tumour type

Supratentorial tumours are commonly associated with seizures, whilst infratentorial tumours are very rarely associated with seizures. Combining the two categories of tumour type would unacceptably underestimate the risk of seizures from supratentorial tumours, and overestimate the risk of seizures from infratentorial tumours.

Supratentorial tumours are further subdivided into brain tumour subtypes with distinct aetiologies, prognoses/life expectancy, reported seizure risk, and type of management that is relevant to the efficacy and safety of ASM treatment (Li 2022; Louis 2021; Weller 2021). The chosen subtypes still represent the most prevalent groups of brain tumour: metastases represent 30% to 50% of all brain tumours – with primary high grade representing approximately 30%, primary low grade approximately 6%, and meningioma approximately 36% of remaining brain tumours (Ostrom 2019; Wanis 2021). We have grouped primary cerebral lymphoma with high grade primary brain tumours due to their low prevalence (approximately 3% of primary tumours) and similar prognosis and seizure risk.

Tumour type will be grouped as follows.

- Supratentorial tumours
  - Diffusely infiltrative high-grade primary brain tumours (WHO Grade 3 to 4 gliomas, including CNS lymphoma) – seizure risk 40-60%
  - Diffusely infiltrative low-grade primary brain tumours (WHO Grade 1 to 2 gliomas)
  - Non-diffusely infiltrative low-grade primary brain tumours (including pilocytic astrocytomas, glioneuronal tumours, ependymal tumours, embryonal tumours, pineal tumours) – seizure risk 65% to 90%
  - Cerebral metastases
  - Meningioma
- Infratentorial tumours and pituitary adenomas

3. Neurosurgical intervention

Seizures may be provoked by the presence of the brain tumour itself, or from surgical intervention and its potential complications (Chen 2018). Postoperative bleeding, infection, infarction and vascular injury may provoke seizures (Chen 2017). While these postoperative events are more likely to occur with more invasive treatment such as resection or debulking, they may still occur after less invasive diagnostic biopsies. The additional risk of seizures related to surgery is thought to be short term (typically within 30 days of surgery). Conversely, in the longer term, surgical resection/debulking is typically associated with a reduction in seizure risk (Chang 2008; Le 2023; Li 2022).

Neurosurgical intervention for brain tumour will be grouped as follows.

- Surgical resection/debulking
- Biopsy
- No neurosurgical intervention

Study follow-up time will be grouped as follows.

- Short term (< 30 days)
- Long term (> 30 days)

Additional features affecting treatment strategy

We will analyse the following characteristics as subgroups and present them as supplementary material. The below characteristics are key factors that influence the treatment strategy (radiation, chemotherapy and surgery) for brain tumours. Additionally, patient sex is a factor that influences ASM use.

- Age (grouped as 18 to 64 years or ≥ 65 years)

- Sex (grouped as male or female)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (grouped as 0 to 2 or 3 to 4). This is a widely used scale that classifies a patient according to their functional baseline; a score of zero being fully active, three being capable of only limited self-care, and five as deceased (Oken 1982).

We prefer to be inclusive and prespecify all known relevant sources of clinical heterogeneity to avoid post hoc analyses where possible. We are aware of the increase in the probability of Type I statistical error and, if we are able to perform multiple subgroup analyses, will interpret the results accordingly.

We will discuss the potential sources of any clinical or statistical heterogeneity narratively, and assess subgroup analyses using the formal test for subgroup interactions in Review Manager (RevMan 2025).

Sensitivity analysis

To assess the possible need for exclusion of studies with high risk of bias and studies with missing data, we will carry out sensitivity analyses. If possible, we will perform a sensitivity analysis of the primary outcome of the review based on the methodological quality of the studies, restricting meta-analysis to only studies with a low risk of bias in all domains (Higgins 2022).

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for the primary and secondary outcomes for the main comparison of ASMs (all subtypes pooled together) versus placebo or no active treatment.

We will include the following outcomes in the table.

1. The number of participants in a treatment group experiencing a first seizure within the study period
2. Adverse events (as reported in the included studies) at any time after the introduction of treatment
3. Health-related quality of life (QoL)
4. Proportion of participants who died within the study period

We will assess the certainty of evidence using the GRADE approach (Schünemann 2013), using the five GRADE domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias). We will justify all decisions to downgrade the quality of evidence by using footnotes, and will add comments to aid the reader's understanding of the review where necessary.

Two review authors (MAM and AB) will independently assess the certainty of the evidence, with any disagreements resolved by discussion or consensus with a third review author (GM), if required.

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Editorial contributions

The Cochrane Epilepsy Group supported the authors in the development of this Cochrane review protocol. The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor-in-Chief, Cochrane Evidence Production and Methods Directorate
- Managing Editor (selected peer-reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Lasse Dührsen, Department of Neurosurgery, UKE, Germany (clinical review); Jennifer Hilgart, Cochrane (methods review); Jo Platt, Central Editorial Information Specialist (search review).

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APPENDICES

Appendix 1. MEDLINE search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2022).

1. exp Brain Neoplasms/

2. exp Glioma/

3. exp Astrocytoma/

4. exp Oligodendroglioma/

5. exp Ependymoma/

6. exp Meningioma/

7. exp Skull Base Neoplasms/

8. (glioma$ or astrocytoma$ or oligodendroglioma$ or ependymoma$ or meningioma$ or skull base neoplasm$).mp.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. (brain or cerebra$ or astrocyte$ or oligodendrog$ or ependym$ or glial or skull base or choroid plexus or neuroepithel$ or neuronal or neuronal-glial or pineal$ or embryonal or haemopoietic or hemopoietic or germ cell$ or mening$ or sella$ or central nervous system or CNS).mp.

11. (cancer$ or tumor$ or tumour$ or malignan$ or carcinoma$ or neoplasm$ or metasta$).mp.

12. 10 and 11

13. 9 or 12

14. Epilepsy/pc [Prevention & Control]

15. Seizures/pc [Prevention & Control]

16. exp Preventive Medicine/ or (prophyla$ or prevent$).mp.

17. (epilep$ or seizure$ or convuls$).mp.

18. 16 and 17

19. 14 or 15 or 18

20. 13 and 19

21. exp *Epilepsy/dt [Drug Therapy]

22. exp Seizures/dt [Drug Therapy]

23. exp Anticonvulsants/

24. (antiepilep$ or anti-epilep$ or anticonvulsant$ or anti-convulsant$ or antiseizure$ or anti-seizure$ or AED or AEDs).mp.

25. exp Midazolam/

26. (Dalam or Dormicum or Dormire or Epistatus or Fulsed or Garen or Hypnovel or Ipnovel or Midazolam* or Nocturna or Setam or Terap or Versed).mp.

27. exp Methazolamide/

28. (Methazolamid* or Methylacetazolamide or Neptazane).mp.

29. exp Propofol/

30. (Anepol or Diprivan or Disoprivan or Disoprofol or Fresofol or Hypro or Lipuro or Plofed or Profol or Propofil or Propofol* or Propolipid or Propovan or Propoven or Provive or Recofol).mp.

31. exp Temazepam/

32. (Dasuen or Euhypnos or Hydroxydiazepam or Levanxol or Methyloxazepam or Nocturne or Norkotral or Normison or Normitab or Nortem or Oxydiazepam or Planum or Pronervon or Remestan or Restoril or Signopam or Temaze or Temazep* or Temtabs or Tenox).mp.

33. exp Thiopental/

34. (Bomathal or Farmotal or Nesdonal or Penthiobarbit* or Pentothal or Sodipental or Thiomebumal or Thionembutal or Thiopent* or Tiobarbital or Tiopental* or Trapanal).mp.

35. (Acemit or Acetamide or Acetazolamid* or Avva or Azm or Azol or Diacarb or Diamox or Diazomid or Diluran or Edemox or Glaupax).mp.

36. Barbexaclon*.mp.

37. (Beclamid* or Chloracon or Hibicon or Posedrine or Nydrane or Seclar).mp.

38. Brivaracetam*.mp.

39. Bromide*.mp.

40. (Carbamazepin* or Carbamazepen* or Carbamezepin* or CBZ or SPD417 or "Apo-Carbamazepine" or Atretol or Biston or Calepsin or Carbagen or Carbatrol or Carbazepin* or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotop or "Novo-Carbamaz" or "Nu-Carbamazepine" or Sirtal or Stazepin* or "Taro-Carbamazepine" or Tegretal or Tegretol or Telesmin or Teril or Timonil).mp.

41. (Carisbamat* or Comfyde or "RWJ-333369" or "YKP 509").mp.

42. (cenobamat* or Xcopri or YKP3089).mp.

43. (Chlormethiazol* or Distraneurin).mp.

44. (Aedon or Anxirloc or Castilium or Chlorepin or Clarmyl or Clobam or Clobamax or Clobator or Clobazam* or Clofritis or Clopax or Clorepin or Frisium or Grifoclobam or Karidium or Lucium or Mystan or Noiafren or Onfi or Sederlona or Sentil or Urbadan or Urbanil or Urbanol or Urbanyl).mp.

45. (Antelepsin or Antilepsin or Chlonazepam or Cloazepam or Clonazepam* or Clonex or Clonopin or Iktorivil or Klonopin or Kriadex or Landsen or Paxam or Petril or Ravotril or Rivatril or Rivotril or "ro 5-4023" or "ro 54023").mp.

46. (Calner or Clorazepat* or Justum or Mendon or "Novo-Clopate" or Tranxene or Tranxilium).mp.

47. (Diapam or Diastat or Diazemuls or Diazepam* or Nervium or Relanium or Valium).mp.

48. (Dimethadion* or Dimethyloxazolidinedione).mp.

49. (Eslicarbazepin* or Exalief or Stedesa or Zebinix).mp.

50. (Esilgan or Estazolam* or Eurodin or Nuctalon or Prosom or Tasedan).mp.

51. Ethadion*.mp.

52. (Aethosuximid* or Emeside or Ethosucci* or Ethosuxide or Ethosuximid* or Etosuximid* or Zarontin).mp.

53. (Ethotoin* or Peganone).mp.

54. (Felbamat* or Felbatol or Felbamyl or Taloxa).mp.

55. (Flunarizin* or Sibelium).mp.

56. (Cerebyx or Fosphenytoin* or Prodilantin).mp.

57. (Gabapentin* or Aclonium or Fanatrex or Gabapetin or Gabarone or GBP or Gralise or Neogab or Neurontin or "Novo-Gabapentin" or Nupentin).mp.

58. ("CCD-1042" or Ganaxolon*).mp.

59. (Erlosamide or Harkoseride or Lacosamid* or Vimpat).mp.

60. (Lamotrigin* or Elmendos or Epilepax or "GW 273293" or Lamictal or Lamictin or Lamitor or Lamitrin or Lamogine or Lamotrine or LTG).mp.

61. (Levetiracetam* or Keppra or LEV or Levitiracetam).mp.

62. (Ativan or Intensl or Loraz or Lorazepam* or Lormetazepam* or Temesta).mp.

63. Losigamon*.mp.

64. ("Magnesium sulfat*" or "Magnesium sulphat*").mp.

65. (Medazepam* or Nobrium or Rudotel or Rusedal).mp.

66. (Mephenytoin* or Mesantoin).mp.

67. (Dapaz or Equanil or Meprobamat* or Meprospan or Miltown or Tranmep or Visano).mp.

68. (Celontin or Mesuximid* or Methsuximide or Petinutin).mp.

69. (Mephobarbit* or Mebaral or Mephyltaletten or Methylphenobarbit* or Metilfenobarbital or Phemiton or Prominal).mp.

70. (Erimin or Nimetazepam*).mp.

71. (Alodorm or Arem or Insoma or Mogadon or Nitrados or Nitrazadon or Nitrazepam* or Ormodon or Paxadorm or Remnos or Somnite or Pacisyn).mp.

72. (Oxcarbazepin* or Actinium or Barzepin or Carbox or Deprectal or "GP 47680" or Lonazet or OCBZ or Oxalepsy or OXC or Oxcarbamazepine or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepine or Prolepsi or Timox or Trexapin or Trileptal or Trileptin).mp.

73. Paraldehyd*.mp.

74. Paramethadion*.mp.

75. (E2007 or Fycompa or Perampanel*).mp.

76. Phenacemid*.mp.

77. (Ethylphenacemid* or Pheneturid*).mp.

78. (Adonal or Aephenal or Agrypnal or Amylofene or Aphenylbarbit or Aphenyletten or Barbenyl or Barbinal or Barbiphen* or Barbipil or Barbita or Barbivis or Barbonal or Barbophen or Bardorm or Bartol or Bialminal or "Blu-Phen" or Cabronal or Calmetten or Calminal or Cardenal or Chinoin or Codibarbita or Coronaletta or Cratecil or Damoral or Dezibarbitur or Dormina or Dormiral or Dormital or Doscalun or Duneryl or Ensobarb or Ensodorm or Epanal or Epidorm or Epilol or Episedal or Epsylone or Eskabarb or Etilfen or Euneryl or Fenbital or Fenemal or Fenobarbital or Fenosed or Fenylettae or Gardenal or Gardepanyl or Glysoletten or Haplopan or Haplos or Helional or Hennoletten or Henotal or Hypnaletten or Hypnette or "Hypno-Tablinetten" or Hypnogen or Hypnolone or Hypnoltol or Hysteps or Lefebar or Leonal or Lephebar or Lepinal or Lepinaletten or Linasen or Liquital or Lixophen or Lubergal or Lubrokal or Lumen or Lumesettes or Lumesyn or Luminal or Lumofridetten or Luphenil or Luramin or Molinal or Neurobarb or Nirvonal or Noptil or "Nova-Pheno" or Nunol or Parkotal or PB or Pharmetten or "Phen-Bar" or Phenaemal or Phenemal* or Phenobal or Phenobarbit* or Phenobarbyl or Phenoluric or Phenolurio or Phenomet or Phenonyl or Phenoturic or Phenylethylbarbit* or Phenylethylmalonylurea or Phenyletten or Phenyral or Phob or Polcominal or Prominal or Promptonal or "Seda-Tablinen" or Sedabar or Sedicat or Sedizorin or Sedlyn or Sedofen or Sedonal or Sedonettes or Sevenal or Sinoratox or Solfoton or "Solu-Barb" or Sombutol or Somnolens or Somnoletten or Somnosan or Somonal or Spasepilin or Starifen or Starilettae or Stental or Talpheno or Teolaxin or Teoloxin or Thenobarbital or Theoloxin or Triabarb or Tridezibarbitur or Triphenatol or Versomnal or Zadoletten or Zadonal).mp.

79. Phensuximid*.mp.

80. (Aleviatin or Antisacer or Auranile or Causoin or Citrullamon or Citrulliamon or Comital or Comitoina or Convul or Danten or Dantinal or Dantoin* or Denyl or "Di-Hydan" or "Di-Lan" or "Di-Phetine" or Didan or Difenilhidantoin* or Difenin or Difetoin or Difhydan or Dihycon or Dihydantoin or Dilabid or Dilantin* or Dillantin or Dintoin* or Diphantoin or Diphedal or Diphedan or Diphenat or Diphenin* or Diphentoin or Diphentyn or Diphenylan or Diphenylhydantoin* or Diphenylhydatanoin or Ditoinate or Ekko or Elepsindon or Enkelfel or Epamin or Epanutin or Epasmir or Epdantoin* or Epelin or Epifenyl or Epihydan or Epilan or Epilantin or Epinat or Epised or Eptal or Eptoin or Fenantoin or Fenidantoin or Fenitoin* or Fentoin or Fenylepsin or Fenytoin* or "Gerot-epilan-D" or Hidan or Hidant* or Hindatal or Hydant* or Ictalis or Idantoi* or Iphenylhydantoin or Kessodanten or Labopal or Lehydan or Lepitoin or Lepsin or Mesantoin or Minetoin or "Neos-Hidantoina" or Neosidantoina or Novantoina or Novophenytoin or "Om-hidantoina" or "Om-Hydantoine" or Oxylan or Phanantin* or Phenatine or Phenatoine or Phenhydan* or Phenitoin or Phentoin or Phentytoin or Phenytek or Phenytex or Phenytoin* or PHT or Ritmenal or Saceril or Sanepil or Silantin or Sinergina or Sodanthon or Sodanto* or Solantin or Solantoin or Solantyl or Sylantoic or Tacosal or Thilophenyl or TOIN or Zentronal or Zentropil).mp.

81. (Lyrica or Pregabalin*).mp.

82. (Mysoline or Primidon* or Sertan).mp.

83. (Gabrene or Garene or Halogabide or Halogenide or Progabid*).mp.

84. (Ecovia or Remacemid*).mp.

85. ("D-23129" or "D23129" or EZG or Ezogabin* or Retigabin* or RTG or Trobalt or Potiga).mp.

86. (Rilutek or Riluzol* or Trifluoromethoxybenzothiazol*).mp.

87. (Inovelon or Rufinamid* or Xilep).mp.

88. Seletracetam*.mp.

89. (Diacomit or Stiripentol*).mp.

90. (Sulthiam* or Sultiam* or Ospolot).mp.

91. Talampanel*.mp.

92. (Tiagabin* or Gabitril).mp.

93. Tiletamin*.mp.

94. (Topiramat* or Qudexy or Tipiramate or Topamax or "Topiramic acid" or TPM).mp.

95. (Tridione or Trimethadion*).mp.

96. Valnoctamid*.mp.

97. (Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or Divalprax or Divalproex $ or DPA or Encorate or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valance or Valcote or Valparin or Valpro$ or VPA or Zalkote).mp.

98. (Depamide or Valpromid*).mp.

99. (GVG or Sabril or Vigabatrin*).mp.

100. (Zonisamid* or Exceglan or Excegram or Excegran or ZNS or Zonegran).mp.

101. or/21-100

102. 20 and 101

103. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

104. clinical trials as topic.sh.

105. trial.ti.

106. 103 or 104 or 105

107. exp animals/ not humans.sh.

108. 106 not 107

109. 102 and 108

110. remove duplicates from 109

CONTRIBUTIONS OF AUTHORS

GKM conceived the project idea and set up the review team.
NM and LW drafted the manuscript and contributed equally to this work as joint first authors.
SN provided methodological input.
All authors (NM, LMW, MAM, MS, MDJ, AGM, RZ, SN, GKM) reviewed the protocol, contributed to manuscript revisions and approved the final version.

DECLARATIONS OF INTEREST

LW: has declared that they have no conflict of interest.

NM: has declared that they have no conflict of interest.

MAM: has declared that they have no conflict of interest.

MS: has declared that they have no conflict of interest.

MDJ: is the chief investigator on the STOP 'EM trial (Surgeons Trial of Prophylaxis for Epilepsy in Meningioma), which is funded by the National Institute for Health and Care Research (NIHR). The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care.

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RZ: has declared that they have no conflict of interest.

SJN: has declared that they have no conflict of interest.

GKM: declares i) an Angelini grant paid to the University of Liverpool as co-applicant on the PROPEL - A multi-method PRoject to maximise efficient and equitable pathways tO suPport from a rEgional epiLepsy centre study (IRIS 183123), which is unrelated to the submitted work; ii) Honoraria paid to the University of Liverpool for delivering a lecture at an educational event sponsored by Angelini, which was unrelated to the submitted work.

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