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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is primary prevention with antiepileptic drugs effective in brain tumors or brain metastases?

Authors: Diego Lobos-Urbina**[1,2]**, Lucas Kittsteiner-Manubens**[1,2]**, José Peña**[2,3,4]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.
[2] Proyecto Epistemonikos, Santiago, Chile.
[3] Departamento Hemato-Oncología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.
[4] Centro de Cáncer Nuestra Señora de la Esperanza, Red de Salud UC-Christus, Santiago, Chile.

E-mail: jepena@uc.cl

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Abstract

Patients with brain tumors –primary or metastatic- have an increased risk of presenting seizures during the course of their disease. So, prophylactic antiepileptic drugs have been proposed. However, the effects of this intervention are not yet clear. To answer this question, we searched in Epistemonikos database, which is maintained by screening multiple databases. We identified 12 systematic reviews including 80 studies overall. Twelve corresponded to randomized trials, but only two answered the question of interest. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE method. We concluded primary prevention with antiepileptic drugs might not reduce the risk of seizures, and it is associated to frequent adverse effects.

Problem

Up to 60% of patients with brain tumors develop seizures. Various mechanisms have been proposed for this; neoplastic tissue could be the starting site of a seizure, especially if it is neural tissue, and on the other hand, intracranial lesions could alter both structurally and functionally the adjacent territory by causing edema, vascular insufficiency, inflammation or releasing metabolically active molecules that promote epileptic activity. It is proposed that the location of the lesions could also influence the onset of seizures, being the incidence higher in cortical lesions.

This summary seeks to answer if primary prevention with antiepileptic drugs is effective in patients that will not be subject to surgery.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Primary prevention with antiepileptic drugs might not decrease the risk of seizures in patients with brain tumors or cerebral metastases, but the certainty of the available evidence is low.
- The use of antiepileptic drugs is associated to frequent adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 12 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12] that include 80 primary studies [13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36], [37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78],[79],[80],[81],[82],[83],[84],[85],[86],[87],[88],[89],[90],[91],[92], twelve of which are randomized controlled trials [13],[14],[17],[22],[23],[36],[42],[65],[84],[86],[91],[92]. Ten of the latter were not used for analyses in this summary because they evaluated patients that would be subject to surgery [17],[22], [23],[36],[42],[65],[84],[86],[91],[92], so only two randomized trials correspond to direct evidence and answer our question[13],[14].
What types of patients were included	Both trials included patients older than 18 years of age, without any previous history of seizures, with diagnosis of primary brain tumor (28.2%) or cerebral metastases (71.8%) and who were not subject to surgery. None of the trials reported the location of the lesions. One trial [13] included people with less than a month from diagnosis, and the other trial [14] included patients with less than 14 days from the time of diagnosis. No trial reported the treatment for the underlying disease.
What types of interventions were included	One trial [13] administered for primary prevention 15 mg/kg of phenytoin orally as an initial dose, followed by 5mg/kg/day orally. They followed the patients for 5.4 months. One trial [14] used valproate with a target serum level of 50-100 µg/mL, and followed the patients for seven months. One trial compared the intervention against placebo [14] and the other did not give any treatment to the control group [13].
What types of outcomes were measured	The main outcome reported was the incidence of seizures. Other reported outcome was the incidence of adverse effects such as nausea, vertigo, myelosuppression, blurred vision, rash and ataxia. No trial evaluated quality of life or mortality.

Summary of findings

The information regarding the effects of antiepileptic drugs for primary prevention in brain tumors or brain metastases is based on two randomized trials [13],[14], which include 174 patients. Both trials measured the onset of seizures and the presence of adverse effects. No trial evaluated mortality or quality of life.

The summary of findings is:

- Primary prevention with antiepileptic drugs might not decrease the risk of seizures in patients with brain tumors or cerebral metastases, but the certainty of the evidence is low.
- The use of antiepileptic drugs is associated to frequent adverse affects. The certainty of the evidence is high.

Antiepileptic drugs as primary prevention in patients with brain tumors				
Patients	Patients with brain tumors			
Intervention	Antiepileptic drugs			
Comparison	Placebo or no treatment			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT antiepileptic drugs	**WITH antiepileptic drugs**		
	Difference: patients per 1000			
Absence of seizures**	264 per 1000	290 per 1000	RR 1.1 (0.66 to 1.82)	⨁⨁◯◯[1] Low
	Difference: 26 patients more per 1000 (Margin of error: 96 less to 216 more)			
Adverse effects***	The information regarding adverse effects in the identified trial is very vague. (RR 7.15; 95% CI 0.48 to 105.95). Nonetheless, there is vast evidence that supports its existence in other contexts [93].		--	⨁⨁⨁⨁[2] High

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT antiepileptic drugs** is based on the risk in the control group of the trials. The risk **WITH antiepileptic drugs** (and its margin of error) is calculated from relative effect (and its margin of error).
**The absence of seizures was evaluated through the follow up time specified for each trial.
***The adverse effects evaluated are described in the initial table.

[1] The certainty of the evidence was diminished for imprecision of the effect estimate.
[2] The adverse effects of antiepileptic drugs in other populations are clearly demonstrated, and nothing suggests they would not be present in this population.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The conclusions of the present summary apply to adult patients with brain tumors (primary or metastases), that are not subject to surgery and who have not had previous seizures.

About the outcomes included in this summary

- The outcomes included in this summary are those that were considered by the authors as critical for decision-making process.
- It was intended to include mortality and quality of life outcomes, but they were not reported in the identified trials.

Balance between benefits and risks, and certainty of the evidence

- It is not posible to make a balance between benefits and risks because the certainty of the evidence regarding the benefits is low.
- Nonetheless, it is reasonable to assume that an intervention that could not have effects on the onset of seizures and has adverse effects would have a negative balance.

What would patients and their doctors think about this intervention

- While many patients and doctors should be inclined against the use of this intervention with the evidence presented in this summary, there are factors that would probably introduce great variation in the real decision-making process. For example, this intervention is usually indicated by doctors in up to 25% of the cases, based on the pathophysiology behind the intervention. In fact, it is common to give antiepileptic drugs to patients with lesions in the brain cortex [94]. It is likely that, given the limitations of the presented evidence, many doctors would not be inclined to modify this conduct.
- It is especially important to inform the patient about the existing uncertainty.

Resource considerations

- It is not possible to make a cost-benefit evaluation due to the uncertainty of the existing evidence.
- Probably this factor will not be the most relevant for the decision, because even though the intervention has a low cost, any potential benefit still needs to be proved.

Differences between this summary and other sources

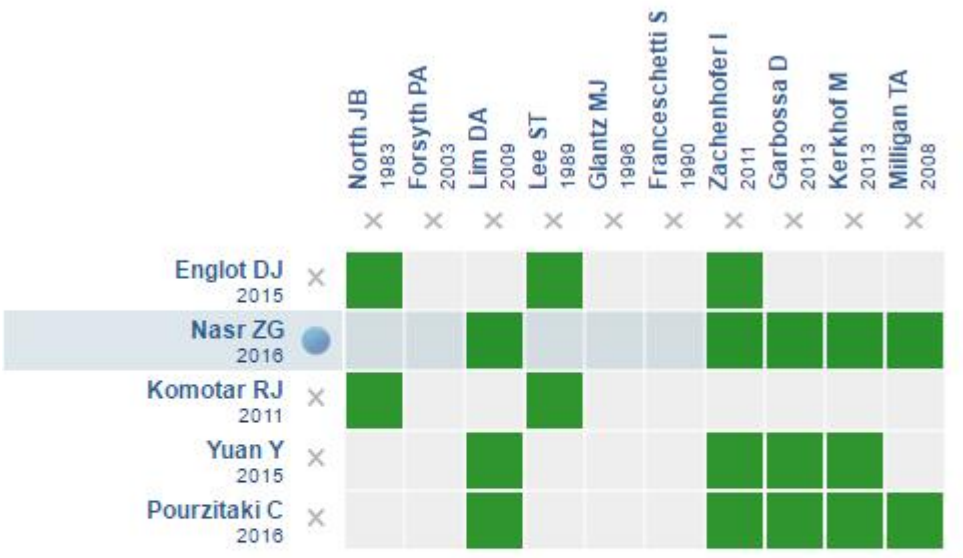
- The conclusions of this summary partially agree with most of the identified reviews, which pose there is high uncertainty, there is a lack of evidence [1],[4], or that it is not recommended because there is no benefit in the intervention [2],[3],[5],[10]. Only one review says that some antiepileptic drugs could have a benefit when used as primary prevention, and base this conclusion on observational studies [11].
- The conclusions of this summary agree with the clinical guidelines. The National Comprehensive Cancer Network guideline [95] recommends not to use antiepileptic drugs as primary prevention in these patients, and so does the European Handbook of Neurological Management [96].

Could this evidence change in the future?

- The probability of this evidence changing in the future is high because the certainty of the evidence is low or very low, mainly due to the scarce amount of primary studies available.
- We searched the WHO International Clinical Trials Registry Platform, and found no ongoing trials about this topic.
- We did not found trials in PubMed database that were not included in the identified systematic reviews.
- It is important to note there are no trials comparing the efficacy of new antiepileptic drugs against placebo for primary prevention. These drugs, by not interacting with the patient's underlying treatment might have a beneficial effect.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Antiepileptic drugs for patients with brain tumors

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.
Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile