Research protocol

GENESIS study
Generating Evidence on NonEpileptic, Stereotypical and Intermittent Symptoms (NESIS)
in chronic subdural hematomas

3.0 version
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Summary
Patients presenting with transient neurological symptoms in the context of subdural hematoma may present a diagnostic challenge. Many of these patients end up with a probable diagnosis of epilepsy (or acute symptomatic seizures), despite a negative electroencephalogram. We believe that the origin of these transient neurologic symptoms in a significant subpopulation of these patients may in fact be cortical depolarization, rather than epileptiform activity. Very specific characteristics have already been identified that differentiate these patients from those who ultimately have epilepsy. The NESIS entity (nonepileptic, stereotypical, and intermittent symptoms) has been proposed to represent this group of patients. A NESIS score was then designed to help distinguish patients with epileptiform activity (confirmed by EEG) from those likely to have cortical depolarization. In other diseases presenting cortical depolarizations, certain antiepileptic treatments (including Topiramate) have already been recognized as effective. We therefore want to perform a prospective, multicenter, randomized-controlled study (Topiramate group and Levetiracetam group) to determine whether a significant difference in the response to treatment exists between Topiramate and Levetiracetam in the NESIS group compared to the non-NESIS group. In addition, in a few eligible patients, we will implant electrocortigography electrodes to demonstrate the existence of cortical depolarizations.

Abbreviations
- CHUS : Centre Hospitalier Universitaire de Sherbrooke
- ECoG : Electrocorticography
- EEG : Electroencephalogram
- SDH : Subdural hematoma
- HSDC : Hémorragie sous-durale chronique
- LEV : Levetiracetam
- LTG : Lamotrigine
- NESIS : Non-epileptic, stereotyped, intermittent syndrome
- TNS : Transient neurological symptoms
- TPM : Topiramate
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Introduction

Problematic

Subdural hematomas (SDH) represent a major problem in the healthcare system, with a reported incidence of 14.1 to 20.6 / 100,000 patients each year\textsuperscript{1,2}. Several have no indication for surgery, but still present significant complications for patients with significant implications for the health system. Transient neurological symptoms (TNS) are one of those complications frequently encountered by neurologists and neurosurgeons. Many of these patients will be diagnosed with induced focal epilepsy, despite often negative investigations (electroencephalogram (EEG)). In the literature, epilepsy is reported in nearly 25% of post-evacuating patients for SDH\textsuperscript{3}.

According to the clinical experience of our community, at the Centre Hospitalier Universitaire de Sherbrooke (CHUS), many patients with TNS and SDH do not correspond to what one would expect focal epileptic seizures. In fact, the number of negative EEG in these patients appears to be greater than the 50%\textsuperscript{4} rate found in the literature of epilepsy in a corresponding population and the same is true for the response rate to antiepileptics which seems less than the usual expected rate of 70%\textsuperscript{4}.

It was therefore important to determine whether an entity distinct from epilepsy could be the cause of the transient neurological symptoms in subdural hematomas. A first retrospective study evaluating patients with SDH and TNS, who presented at the CHUS from 1996 to 2017\textsuperscript{5} was initially completed by our research team. Fifty-nine patients (39 cases (EEG +) and 20 controls (EEG -)) were included in the study and analyzed. Dysphasia and prolonged neurologic episodes (more than 5 minutes) were associated with negative EEG, while clonic movements, altered consciousness, positive symptoms, complete response to antiepileptics, and mortality were associated with positive EEG (p <0.001). These data, combined with an exhaustive review of the literature, allowed us to conclude that an entity other than epilepsy, at the origin of these distinctions, probably existed, and to propose the term NESIS (nonepileptic, sterotypical, and intermittent symptoms) to distinguish it. Subsequently, the NESIS score (see appendix 1) was designed with the distinctions described above, with a score of ≥4 predicting with a sensitivity of 96.6% and a specificity of 100% the group to which a patient belongs\textsuperscript{5}.

Then, we wanted to evaluate in a preliminary and retrospective way the incidence of this syndrome in the population of chronic SDH (cSDH). A descriptive and retrospective study aimed at comparing groups based on the NESIS score was then started. This study identified 22 patients from 2016 to 2018 who presented to the CHUS with TNS in the context of cSDH. Of these, 13 (59%) had a NESIS score of 4 or more. Particularly interestingly, and consistent with the initial hypotheses developed in relation to the existence and pathophysiology of NESIS, the NESIS and non-NESIS groups had significantly different responses to treatments. In fact, the response to standard antiepileptics (resolution of TNSs) was 100% in the non-NESIS group (probable epilepsy) compared to 14% in the NESIS group (p = 0.02, Fisher's exact test). In addition, 100% of patients in the
NESIS group who did not respond to standard antiepileptics responded with Topiramate or Lamotrigine (LTG) (2 antiepileptic treatments recognized for their impact on cortical depolarization) (article in process of submission, unpublished data)\textsuperscript{28}.

Following this preliminary study which described a significant difference in the response to treatment of TNS depending on the type of antiepileptic drug used and the NESIS score obtained, it is now more than relevant to validate this difference through a prospective randomized study. Indeed, a significant difference between the efficacy in the drugs studied and the NESIS groups would make it possible to offer a new therapeutic avenue for NESIS patients who do not seem to respond to usual treatments in addition to validating the existence of this new entity (NESIS). On the other hand, a better response to certain drugs known to have an incisive impact on cortical depolarization in the NESIS subgroup would strengthen the hypothesis of cortical depolarizations as a pathophysiological phenomenon underlying the NESIS entity. Prospective identification of these patients would also make it possible to better characterize the pathophysiology of symptoms.

**Literature review**

Cortical depressions are massive waves of depolarization propagating at a rate of 2-9 mm/minute through gray matter\textsuperscript{6}. They are caused by a sudden and sustained alteration of balance of transmembrane ion gradients, a release of neurotransmitters, an increase in energy metabolism and ultimately a decrease in electrical activity. Cortical depressions are now recognized in various pathologies such as subarachnoid hemorrhages, migraines, head trauma and intra-parenchymal hemorrhages\textsuperscript{7}.

As migraines are frequent, the phenomenon of cortical depression has been further studied in this situation. In fact, it was in migraines that the phenomenon was first described in 1942 by Laeo. 20-30\% of migraine sufferers have auras (in any form). These auras are in fact the clinical manifestation of cortical depression\textsuperscript{8}. Several antiepileptics, including Topiramate (TPM), are used for migraine prophylaxis. TPM is known to have different mechanisms making it effective against migraines\textsuperscript{9}. It is thought to act by modulating voltage-gated sodium and calcium channels, by potentiating the inhibition of GABA-a and by blocking the excitatory effect of glutamate\textsuperscript{9}. Regarding the efficacy of Topiramate in migraine headaches, a meta-analysis of 2012\textsuperscript{10} identified four class 1 studies and seven class 2 studies, all demonstrating significant efficacy of TPM compared to placebo\textsuperscript{12,13,14,15,16,17}. In addition, despite a monthly reduction in the frequency, intensity and duration of migraines in the Propanolol and Topiramate groups, the TPM group reported a significantly greater mean reduction than the Propanolol group\textsuperscript{18}. In the other hand, Levetiracetam (LEV) reports more conflicting data. In fact, a 2011 randomized-controlled study showed no benefit of LEV in migraine (n = 96)\textsuperscript{19}. In contrast, another randomized-controlled study from 2013 was able to demonstrate a significant reduction in migraines (n = 65), however, the large number of losses at follow-up, more in the LEV group than in the placebo group, makes this result difficult to interpret according to several authors\textsuperscript{20}.
Some more fundamental studies have also evaluated the response to antiepileptics directly at the level of cortical depressions induced in laboratory. Four studies between 2005 and 2012\textsuperscript{21,22,23,24} have evaluated cortical depressions in rats and cats before and after injection of Topiramate (10 and 30 mg / kg). They have demonstrated a significant dose-dependent reduction in cortical depressions 30 minutes after an injection of Topiramate. Regarding Levetiracetam, a fundamental study from 2017 could not demonstrate his efficacy in the treatment of cortical depressions in the hippocampus of mice\textsuperscript{25}.

Considering the presence of cortical depressions in several irritative brain conditions, we consider that these could also be the cause of NESIS in the context of SDH. Moreover, according to our preliminary studies, NESIS has a better respond to Topiramate and Lamotrigine than to other antiepileptics, treatments which are nevertheless all considered to have similar efficacy\textsuperscript{29} in focal epilepsy. LEV specifically has an efficacy rate judged to be comparable to TPM for the control of epilepsy. A recent study has also demonstrated a response rate of 28\% for TPM compared to 50\% for LEV in a refractory population.\textsuperscript{30} This could be explained by the presence of causal cortical depolarizations in patients with NESIS, with TPM and LTG being proven to be both effective in cortical depolarizations, which is not the case with other common antiepileptics (Levetiracetam, Phenytoin). It therefore becomes relevant to begin the study of this hypothesis, which if confirmed, would offer a new therapeutic avenue for these patients who are usually refractory to standard treatments.

Outcomes
Primary outcome
The aim of this study is to demonstrate the efficacy of Topiramate for patients with transient neurological symptoms in the context of chronic subdural hematomas with a positive NESIS score, in whom usual epilepsy treatment appears to be less effective. For this purpose, the efficacy of Topiramate (shown to be effective in cortical depressions) will be compared with that of Levetiracetam (which has not been shown to be effective in cortical depressions).

Secondary outcomes
- Validate the existence of the NESIS entity: if we manage to demonstrate a significant difference between the response to TPM and LEV in the NESIS group compared to the non-NESIS group, the evidence concerning the existence of a different process at the origin of the NESIS group will then be more numerous. Cortical depolarizations will be the main hypothesis.
- Confirm cortical depolarizations as the main etiology of NESIS by electrocorticography.
- Validate the NESIS score: If we are able to demonstrate a significant difference between the effectiveness of TPM and LEV between the NESIS and non-NESIS...
groups, we will be able to demonstrate the success of the NESIS score in distinguishing patients with TNS into two distinct groups.

Possible scope of conclusions
If our hypotheses are confirmed, in addition to an additional demonstration of the NESIS entity, a treatment targeting cortical depressions could be offered to patients with TNS, cSDH and NESIS score ≥4. In addition, a better knowledge of this syndrome will allow subsequent studies to evaluate other therapeutic avenues having fewer side effects or being more effective, in addition to being able to characterize the course and prognosis of NESIS syndrome in order to avoid diagnostic delay and additional investigations.

Study quote
To meet our objectives, we offer a multicenter, prospective study of randomized-controlled clinical trial type validating therapeutic efficacy.

![Study groups](image)

**Characteristic summary of Topiramate (Topamax)²⁶**
- **Class**: anticonvulsivant.
- **Indications**: Focal and generalized epilepsy, migraine prophylaxis.
- **Mechanisms of action**: Blockage of voltage-gated sodium channels, increased GABA activity, AMPA/glutamate receptor antagonist, weak inhibition of carbonic anhydrase.
- **Dosage**: 50 mg BID, to be increased by 50 mg per week up to 200 mg daily. Can then be increased by 100 mg per week, to a maximum of 400 mg daily.
- **Recommended renal adjustment**: Clearance <70 mL/minute/1.73m²: dose reduction by 50% and slower titration.
- **No adjustment for hepatic insufficiency**.
- **Frequent side effects**: paresthesia, fatigue, dizziness, weight loss, abdominal pain, anorexia, nausea and vomiting.
- **Serious side effects**: depression, nephrolithiasis.
- **Contraindications**: history of hypersensitivity.
- **Interactions**: may increase the depressant effect on central nervous system by other drugs.
Characteristic summary of Levetiracetam (Keppra)²⁷

- **Class**: anticonvulsivant.
- **Indications**: focal and generalized epilepsy, convulsive prophylaxis (perioperative, subarachnoid hemorrhage, head trauma).
- **Dosage**: To be start at 500 mg BID, increase by 500 mg every two weeks to a maximum of 1500 mg BID.
- **Recommended renal adjustment**:
  - Clearance 80-130 mL/minute/1.73m²: 500-1500 mg BID
  - Clearance 50-80 mL/minute/1.73m²: 500-1000 mg BID
  - Clearance 30-50 mL/minute/1.73m²: 250-750 mg BID
  - Clearance 15-30 mL/minute/1.73m²: 250-500 mg BID
  - Clearance <15 mL/minute/1.73m²: 250-500 mg daily (expert opinion)
- **No adjustment for hepatic insufficiency.**
- **Common side effects**: increased blood pressure, behavioral changes, headache, psychotic symptoms, fatigue, dizziness.
- **Serious side effects**: depression, suicidal thoughts.
- **Contraindications**: history of hypersensitivity.
- **Interactions**: may increase the depressant effect on central nervous system by other drugs.

**Placebo**

No placebo will be used, as patients with transient neurological symptoms require treatment with antiepileptics. Topiramate and Levetiracetam are currently approved drugs for the treatment of focal seizures²⁹. We will therefore take TPM as an intervention (drug shown to be the most incisive, to date, in cortical depressions) and LEV as an active control.

**Obtaining treatments for the study**

As TPM and LEV are approved treatments in the treatment of focal seizures and are already acceptable choices for the treatment of patients with transient neurological symptoms, even with negative EEGs, we will treat patients with one or the other of these treatments through a usual prescription that will be taken to the community pharmacy. These two treatments can therefore be approved for reimbursement either by the RAMQ or by private patient insurance. Moreover, since TPM is approved by Health Canada for the treatment of TNS in the context of SDH, even with negative EEG, additional approval by Health Canada will not be necessary³⁰.
Population
Target population
All adult patients with transient neurological symptoms with negative EEG in the context of chronic subdural hemorrhage.

Accessible population
All adult patients presenting to any of the participating centers with transient neurologic symptoms in the setting of cSDH. The study will be multi-center and Sherbrooke will be the coordinating center.

Patients selection – sampling
- All patients presenting to one of the participating centers with transient neurological symptoms in the context of cSDH.
- Convenience non-probability sampling.
- Systematic sampling, recruiting all patients presenting at one of the participating centers, regardless of the time of admission (night, weekend). As all patients presenting with TNS in the setting of cSDH will be eligible for the study, the sample should be representative of the population. Of course, they will be included according to their willingness to participate in the study, so a bias of voluntarism is unmissable.

Inclusion criteria
• ≥ 18 years old
• Chronic subdural hematoma
• Transient neurological symptoms (Sensory, motor, cerebellar or speech symptoms, lasting 6 hours or less)
• Initial negative EEG

Exclusion criteria
- Contraindications to Levetiracetam
  o Psychiatric history (major depression, psychosis, risk of suicide)
  o History of hypersensitivity to LEV (anaphylaxis, angioedema, skin reaction)
- Contraindications to Topiramate
  o History of hypersensitivity to TPM
  o Glaucoma
  o Past nephrolithiasis
- Known epilepsy or seizure before the current subdural hemorrhage
- Actual take of antiepileptic
- Intracranial pathology not caused by SDH (intra-parenchymal hemorrhage, neoplasia)
- Pregnancy or planning to be
- Inability to carry out the necessary follow-ups for the study
- Refusal of the attending physician

Sample size
The studies directly concerning our subject being few or even zero, we decided to calculate our sample size based on two calculations and two types of data (which do not perfectly represent our variables, each in their own way) in order to optimize our chances of obtaining a size approaching the one we need for adequate power.

Based on the means and standard deviations of reduction in cortical depressions with TPM and LEV in the fundamental studies previously described, it is possible for us to calculate the sample size that should allow us to establish a significant difference between our groups, if possible.

Indeed, in the first study verifying the effect of different drugs against cortical depressions in rats, the controls had 14.3 +/- 2 cortical depressions/2 hours. After chronic treatment with TPM, cortical depressions were reduced to 7.8 +/- 2 cortical depressions/2 hours. Then, if we calculate the average reduction in cortical depressions, we get: 14.3 - 7.8 = 6.5. The standard deviations of each adding up, we get 2 + 2 = 4. We therefore have an average reduction of 6.5 +/- 4 cortical depressions/2 hours after treatment with TPM.

Regarding LEV, in a study evaluating the reduction of cortical depressions from various treatments in mice, LEV increased cortical depressions insignificantly (control group having 2.75 +/- 0.34 cortical depressions/minute and LEV group having 5.24 +/- 2.47 cortical depressions/minute). Given a non-significant trend towards an increase in cortical depressions, we will retain that the LEV is not effective and therefore has an average reduction in cortical depressions of 0.

Based on fundamental animal studies, here is the sample size calculation using the means reduction:

\[
N(\text{by group}) = 2 \left[ \frac{(z\alpha + z\beta)\sigma}{\Delta} \right]^2
\]

\[
N = 2 \left[ \frac{(1,960 + 1,282)4}{6.5} \right]^2
\]

\[
N = 8
\]

The number of patients needed per group would therefore be 8. As the values used come from fundamental studies, their validity in humans for the calculation of the sample size is difficult to predict. In addition, since our outcome is a dichotomous variable (resolution or not of symptoms) and not a continuous variable (number of episodes), more patients must be expected to demonstrate a significant difference.

Légende
\( \alpha = 0,05 \) by convention
\( \beta = 0,10 \) by convention
\( \Delta = \) reduction means difference of cortical depressions between TPM and LEV (6,5 – 0 = 6,5)
\( \sigma = \) standard deviation (2 + 2 = 4)
\( Z = \) normalized form of the error according to values constantes sans unités
So, to optimize our chances of getting a sufficient sample size, we also calculate the sample size with a proportion calculation.

In the retrospective study carried out at the CHUS by our research team\textsuperscript{28}, the results of which have not yet been published, the NESIS group had complete resolution of TNS in 14\% when treated with usual antiepileptics. Upon failure of usual treatments and after a change to recognized treatments for cortical depression (Topiramate and Lamotrigine), 100\% of patients had resolution of symptoms. It is important to understand that the treatment of the patients in this study was administered entirely within the hospital, a poorer compliance is therefore to be expected for our patients who will continue their treatment at home, which could affect the power of our study. However, these proportions are still those which come closest to what could be found in our study.

Calculation of sample size from proportions:

\[
2N(\text{by group}) = \frac{4(z\alpha + z\beta)^2\bar{p}(1-\bar{p})}{(pc - pexp)^2}\left(\frac{pc - pexp}{p - \bar{p}}\right)^2
\]

\[
2N(\text{by group}) = \frac{4(1,960 + 1,282)^20,57(1 - 0,57)}{(0,14 - 1)^2}
\]

\[
2N = 14
\]

\[
N = 7
\]

The size calculated with the core studies as well as with the proportions taken in the retrospective study in our center are similar (8 and 7, respectively). In order to prevent a lack of potency for the reasons mentioned above, a slightly larger size will be preferred, and 15 patients seems a reasonable number. This calculation represents the sample size that one should aim for in each group (intervention and active comparator) within the NESIS subgroup. It will therefore be necessary to analyze the results of nearly 30 patients in the NESIS group.

As the non-NESIS patients are not part of our primary outcome and are less numerous than the NESIS (72\% compared to 28\%\textsuperscript{28}), they will be included in the study without a specific target, up to a maximum of 30 patients and their results will be analyzed descriptively.

Considering the dropout or loss rate at follow-up, probably around 30-40\%, a sample of a total of 42 patients with NESIS seems justified. Then, considering that nearly a third of patients will have a NESIS score of less than 4 (non NESIS), 56 patients should be included in the study. Finally, given the number of refusals to participate in the study, probably nearly half of the patients, we plan to approach at least 120 patients.
The final recruitment target is therefore 56 patients (Figure 2).

**Figure 2 – Patients distribution**

![SDH + TNS distribution diagram](image)

**Sample availability**

The number of participants to be randomized is acceptable and feasible but will require a multi-center design. In fact, during the retrospective study at the CHUS from March 2016 to March 2018, 18 patients with TNS in the context of cSDH with negative EEGs were identified. Thus, considering at least 4 centers participating in the study, the inclusion of 56 patients in 3 years seems realistic. Moreover, the NESIS entity being newly recognized (mentioned only since 2018), the incidence of NESIS is probably higher than what was found between 2016-2018, the patients being now more easily identified and classified.

**Patient recruitment**

Patients will initially be identified by neurosurgeons and neurologists from participating centers. These physicians will be aware of the existence of our study and will have the list of inclusion and exclusion criteria. They will therefore be able to inform us when a potential candidate is hospitalized.

These patients will then be seen during an initial visit by the research nurse. This meeting will take place during their hospitalization, in the patients' respective rooms or in a closed room (if multiple bed in the same room) (in order to avoid any external influence on the consent, in addition to better maintaining the confidentiality of the candidates). The purpose of this visit will be to assess the patient's eligibility for the study, to explain the purpose of the study and its interventions. If the patient wishes to participate in the study, a consent form will be read and signed by the patient (Appendix 2). The consent must meet the same criteria as what is applied in the clinic, or a patient must be able and offer free and informed consent. Substituted consent in the event of incapacity (permanent or temporary) with the most significant relative, at the bedside or by telephone will also be authorized. This form will contain the frequent and serious side effects of the two proposed treatments. All the patients who sign will be randomized in the study, into the TPM or LEV group. The method and location of recruitment will therefore be the same for all patients (intervention and active comparator).
Randomization will be made by random block allocation. A number will be assigned to each patient and will be entered into a software that will allow patient randomization, which can be found on the site: https://www.randomizer.at. Patients will be matched there for their NESIS scores (≥4 or <4), their home sites (CHUS or other centers) and the presence of SDH evacuating surgery (yes or no). These factors seem to us to be the ones that could have the greatest impact on the results. When starting the randomization, the software must be blocked in order to allow its use, so no modification of the randomization parameters can be added when the process is going to be started.

As recruitment and randomization take place during hospitalization of patients, no travel or additional testing will be required.

**Sampling bias control**

The use of a multicenter study comprising more than one center, which will be several kilometers apart, will limit the possible geographical and environmental impact on the results of our sample in relation to the target population. In addition, routine screening of all patients presenting with TNS and negative EEG, in the setting of cSDH, regardless of the time of admission, will also ensure a more representative sample of the population.

In order to limit the bias of voluntarism, we have implemented several measures. First, it is important to minimize the number of patients who might decline to participate in the study. For that, we have constructed our study so that participation in the study does not involve additional testing or traveling than is already indicated by the primary pathology. In addition, we will educate patients on the equal effectiveness of the treatments that will be offered in the study and the fact that these two treatments are currently approved for the treatment of their condition. This should be reassuring. In addition, the availability of a member of the research team for any questions or side effects will also be a positive reason to participate. Ultimately, the substituted consent clause will help maintain eligibility for a significant proportion of patients, given the prevalence of confusion and neurocognitive disorder in the population with cSDH.

**Measures to avoid dropouts**

Once the randomization, it will be necessary to minimize the dropouts in order to maintain the random effect of the randomization and therefore a representative sample of the population. To begin with, it will be important to be readily available. Patients will have our contact details and a telephone follow-up will be carried out when problems arise. If necessary, a clinic appointment can be set. When side effects, it will be discussed with the patient to lower the dose, in order to reduce the side effects, before stopping the antiepileptic permanently. Of course, the final decision will be up to the patient.

In addition, the medication will be started in increasing doses, in order to limit side effects.
Limiting clinical appointments to what patients would have had without participating in the study, namely neurology follow-up and neurosurgery follow-up, should also limit dropouts by limiting the involvement required by patients.

Variables and data collection

Initial data
First, several demographic and characteristic data regarding subdural hematomas and transient neurological symptoms will be collected. These data will allow us to assess whether certain factors have an impact on the response to treatment.

<table>
<thead>
<tr>
<th>Table 1 - Demographic data and characterization of subdural hematoma</th>
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<tbody>
<tr>
<td><strong>Demographic data</strong></td>
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<td><strong>Life habits</strong></td>
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<td><strong>Comorbidity</strong></td>
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<td><strong>Past medical history</strong></td>
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<td><strong>Drugs</strong></td>
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<td><strong>SDH type (Nakaguchi classification)</strong></td>
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<td><strong>SDH location</strong></td>
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<td><strong>SDH cause</strong></td>
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<tr>
<td><strong>SDH thickness</strong></td>
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<tr>
<td>Middle line shift</td>
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<td>-------------------</td>
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<tr>
<td>Initial Glasgow score</td>
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</tbody>
</table>
| Draining surgery | Yes  
No |
| Surgery location | Right  
Left  
Both |
| Concomitant subarachnoid hemorrhage | Yes  
No |
| Electroctographic | Yes  
No |
| MRI | Yes  
No  
Particularities |

**Table 2 – TNS characteristics**

| Visual symptoms | Visual loss  
Twinkling light  
Other |
|------------------|-----------|
| Sensory symptoms | Hypoesthesia  
Paresthesias  
Other |
| Motor symptoms | Paresis  
Clonies  
Change in tone  
Other |
| Speech symptoms | Aphasia  
Dysarthria  
Mutism  
Other |
| Cerebellar symptoms | Balance disorder  
Nausea and vomiting  
Dizziness / Vertigo  
Other |
| Altered state of consciousness | Yes or No |
| Duration of symptoms | Minutes |
| Number of episodes | |
| Migration of symptoms | Yes or No |
| Stereotyped symptoms | Yes or No |
| Prodrome | Type |
| Postictal | Yes or No |
| NESIS score at randomization | -8 à 13 |
Variables
Research question: Is Topiramate more effective than Levetiracetam in patients with TNS and negative EEG in the context of SDH, in the NESIS group (increased probability of cortical depolarization), compared to the non-NESIS group (increased likelihood of epilepsy)?

As indicated in our research question, our study mainly aims to verify the effectiveness of TPM (dependent variable) compared to LEV in the NESIS group compared to the non-NESIS group (independent variable). For this, evaluations with standardized questionnaires will make it possible to assess the resolution of neurological symptoms (dichotomous variable). In addition, reductions in the frequency, intensity and duration of TNS will be assessed (continuous variables).

The tolerance of the two study drugs will also be compared. There will be a comparison of the number of failures in the two groups (dichotomous variable) and the percentage of patients with side effects (continuous variable).

Table 3 - Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Measurement method</th>
<th>Measuring instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topiramate efficacy</strong></td>
<td>Complete reduction of neurological symptoms (yes or no)</td>
<td>Medical assessment using a form</td>
</tr>
<tr>
<td></td>
<td>Average reduction in TNS frequency (nb/week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average reduction in TNS duration (minutes)</td>
<td></td>
</tr>
<tr>
<td><strong>Levetiracetam efficacy</strong></td>
<td>Complete reduction of neurological symptoms (yes or no)</td>
<td>Medical assessment using a form</td>
</tr>
<tr>
<td></td>
<td>Average reduction in TNS frequency (nb/week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average reduction in TNS duration (minutes)</td>
<td></td>
</tr>
<tr>
<td><strong>Topiramate tolerance</strong></td>
<td>Type of side effects (e.g. dysphasia, paraesthesia, fatigue, drowsiness, dizziness)</td>
<td>Medical assessment using a form</td>
</tr>
<tr>
<td></td>
<td>Severity of side effects (graded according to CTCAE terminology)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of dropouts (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication deemed useful by the patient (yes or no)</td>
<td></td>
</tr>
<tr>
<td><strong>Levetiracetam tolerance</strong></td>
<td>Type of side effects (e.g. irritability, depression, drowsiness, headache, fatigue)</td>
<td>Medical assessment using a form</td>
</tr>
</tbody>
</table>
Measuring instrument
Our collection data will take the form of a questionnaire. However, the characterization of neurological symptoms requiring some training, in order to be able to adequately distinguish relevant neurological symptoms (those transient likely caused by SDH) from those unrelated to SDH, the main measuring instrument will be a medical evaluation by a person trained in neurology or neurosurgery. This assessment will be based on a questionnaire (appendix 4), so as not to omit the assessment of all areas relevant to the study. Our study being the first on the subject, no questionnaire already approved in other studies can be used. For these reasons, we have constructed a questionnaire including a part on TNS and another on side effects. Doctors or residents evaluating patients won’t forget items and will also be encouraged to further specify the various positive items found during the evaluation.

During the initial visit, a standardized questionnaire including demographic data, characteristics of cSDH and transient neurological symptoms will be completed by a member of the research team using the hospital and patient record (appendix 3). This questionnaire will be administered by a physician, resident or research nurse. We consider that characterization of the current episode at the initial visit will not require full training in neurology or neurosurgery. Indeed, the patient will have already been seen closely by a neurologist or neurosurgeon who will have considered TNS as relevant and secondary to the SDH. However, before administering this questionnaire, the nurse will receive a training, which will be given by a member of the research team.

During follow-ups, by telephone or in clinic, the patient will have in hand his research notebook (appendix 5) in which he will have made a calendar of neurological episodes
that have occurred, or side effects noted. This notebook will limit recall bias and will be analyzed as a secondary outcome, in order to compare the reliability of the information noted by patients with that reported by doctors. Subsequently, an assessment by a resident, neurologist or neurosurgeon will be done using the form described above (appendix 4).

The existence of propagated cortical depolarizations will be assessed by electrocorticography (ECoG) for some operated patients (see below for the detailed procedure) as well as by a surface EEG and a near infrared spectroscopy monitor. These paraclinical examinations will help to rule out a diagnosis of epilepsy and will provide the physiological data necessary for the confirmation of cortical depolarizations.

Side effects will be assessed and graded using CTCAE terminology (Common Terminology Criteria for Adverse Events)\(^3\).

After a first negative pre-randomization EEG, 2 more EEGs will be performed at 24 hour intervals in order to increase the diagnostic sensitivity of ictal activity. If an EEG is positive, there will be no further EEG. These EEG results will help for further validation of the NESIS score.

Magnetic resonance imaging will be recommended in patients with 3 negative EEGs, in order to rule out another structural cause, such as transient ischemic events. This will remain at the discretion of the clinician, depending on clinical relevance and availability of the examination.

**Process**

**Initial meeting**

Patients will be seen during their initial hospitalization following the diagnosis of TNS and their first negative EEG. If SDH evacuating surgery is planned for a patient who has already been randomized, they will be offered the installation of an ECoG monitor during the same surgery. This step will be optional. Subsequently, the patients will be reviewed postoperatively and the intervention will be started if transient neurological symptoms persist.

The meeting will be conducted by a research nurse or a member of the research team. An explanation of the study, drugs, goals, and intended patient involvement will be discussed. At this point, patients will have the choice of whether or not to sign the consent form. They will be given time for reflection, if desired. If the patient is participating in the study, demographic data, clinical characteristics of the subdural hematoma and characteristics of transient neurological symptoms will be collected using a standardized questionnaire (Appendix 3). Thereafter, treatment (TPM or LEV) will be assigned by randomization and started during hospitalization with a planned increase up to
therapeutic doses according to the protocol below. A notebook containing the information discussed, the contact information and forms (appendix 5) for weekly monitoring of neurological symptoms and side effects will be given.

In parallel, after starting the treatment (TPM or LEV), two other daily EEGs will be performed. If an EEG is positive, there will be no further EEG needed. Additionally, if an EEG is positive, the patient will remain in the same treatment group, however, a sub-analysis may compare the correlation between EEG and NESIS score results. In addition, brain magnetic resonance imaging will be recommended for patients with three negative EEGs to rule out an alternative diagnosis, such as transient ischemic events. This test is already part of the usual assessment of transient neurological symptoms with negative EEG and therefore does not represent an additional test for patients. However, this examination will be at the discretion of the clinician, depending on the clinical relevance and availability of the examination.

**Electrocorticography**
If the patient has TNS preoperatively, the installation of electrocorticography electrodes in the subdural space will be suggested. We anticipate that approximately 5 to 10 patients out of the 56 enrolled will be eligible and be offered this option. This step is optional and will not influence subsequent medical treatment. However, it will help to demonstrate the existence of propagated cortical depolarizations and potentially prove the effectiveness of a non-invasive screening strategy. If the patient agrees, two ECoG strip electrodes will be inserted into the subdural space along with the installation of the subdural drain during the surgery. The electrodes will be located at the level of the upper temporal line and oriented anteroposterior in order to cover the frontal operculum as well as the inferior parietal lobule. This procedure is identical to that carried out routinely in the surgical assessment of patients with epilepsy. The patient will then be transferred to the EEG monitoring unit where a surface EEG and a bi-frontal near infrared spectroscopy monitor will be installed. The patient will then be monitored continuously until at least 5 episodes of TNS are recorded, or for a maximum of 72 hours. The electrodes will then be removed by traction at the bedside and a stitch will be performed under local anesthesia. The data will be analyzed by an epileptologist.

**Intervention**
The intervention (Topiramate versus Levetiracetam) will be initiated in the hospital and then, initially, a prescription will be given to the patient for the community pharmacy.

Topiramate will be initiated at 50 mg BID, with an expected increase of 50 mg per week until symptoms are controlled or up to a maximum titration of 100 mg BID.

Levetiracetam will be initiated at 500 mg BID, with an expected increase of 1000 mg divided into 2 doses per week until symptoms are controlled or up to a maximum titration of 1500 mg BID.
The drugs could be reduced or stopped after discussion with a doctor because of side effects or no improvement in TNS.

**Follow-up**

There will be two phone follow-ups (2nd week and 6th month), as well as two clinical follow-ups (2nd and 4th month).

Phone follow-up: Medical evaluation by a resident, neurologist or neurosurgeon participating in the study. The person administering the assessment will follow a standardized questionnaire so as not to omit information relevant to the study. This assessment includes characterization of transient neurological symptoms and investigation of side effects.

Clinical follow-up: The patient will bring his study notebook to the appointment, in which he will have recorded the various TNS or side effects that have occurred in recent weeks. The appointment will be made by a neurologist or a neurosurgeon (all patients will have a meeting with each of the two specialists). The doctor will therefore carry out an evaluation of TNS and side effects, by completing the standardized questionnaire, which will help to limit the missing data.

The last follow-up will take place at 6 months, a date that we have based on the various studies in cortical depression which have demonstrated maximum effectiveness of TPM at 17 weeks. As we did experience in our community, we believe that a significant difference could emerge even earlier.

Losses during follow-up: patients who do not come to the follow-up appointment will be contacted again. In the event of a refusal to attend follow-up or a second absence from an appointment, with the patient's consent, a medical assessment may be completed by phone.

If the patient wishes to stop the antiepileptic drug, a trial of smaller doses of the same treatment will be offered. Upon refusal, or failure despite a reduction in doses, TPM will be offered to the patient if he had LEV and vice versa. This change of group will only be possible after 2 months from the beginning of treatment. These data will not be included in the calculation of the primary outcome, but can still be analyzed as a secondary outcome to assess whether changing patients from one group to another allows them to fully resolve the TNS. Patients who fail both treatments, or who refuse to attempt the treatment in the other group will be excluded from the remainder of the study and treatment with another antiepileptic recognized in the treatment of focal seizures as well as an usual follow-up will be offered.
Participant calendar

<table>
<thead>
<tr>
<th>Recruitment (Day 1)</th>
<th>Randomization (After recruitment)</th>
<th>Phone follow-up (Week 2)</th>
<th>Clinic follow-up (Month 2)</th>
<th>Clinic follow-up (Month 4)</th>
<th>Phone follow-up (Month 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized</td>
<td>Start of treatment</td>
<td>Medical assessment</td>
<td>Medical assessment</td>
<td>Medical assessment</td>
<td>Medical assessment</td>
</tr>
<tr>
<td>questionnaires :</td>
<td>with standardized questionnaire</td>
<td>with standardized</td>
<td>with standardized</td>
<td>with standardized</td>
<td>with standardized</td>
</tr>
<tr>
<td>Epidemiological</td>
<td>EEG daily x 2</td>
<td>questionnaire</td>
<td>questionnaire</td>
<td>questionnaire</td>
<td>questionnaire</td>
</tr>
<tr>
<td>data</td>
<td>MRI if needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Collection method

Sources: Data will be collected initially with the help of the patient's medical record. Subsequently, the rest will be completed entirely by the patient or his family. The evaluations will be guided by standardized questionnaires.

For patients with ECoG, continuous waveforms will be recorded for the entire period the electrode will be implanted, either up to the recording of 5 TNS episodes or up to 72 hours of recording.

The data will be collected double blind. The person administering the questionnaire and the person analyzing the data will not know the patient’s group. In addition, a study number will be assigned to all patients during randomization and this is going to identify the patients on the questionnaires. Thus, the data will be entered into the Excel software anonymously. Following the study, the data will be kept for a period of 25 years, in a file locked with a password that will be in the research nurse’s locked filing cabinet.

Data analysis

Statistics

Statistical analysis of the various data will be done with the help of the Statistical Package for the Social Sciences (SPSS) software. Most of the data will be analyzed by members of the research team. If necessary, the statistician of the CRC (Clinical Research Center) will be consulted.

The results will be analyzed by "intension-to-treat" given the expected dropouts in the two treatment groups.

Primary outcome: To assess the efficacy of TPM compared to LEV in the treatment of TNS in the context of SDH with negative EEG. To do this, it will be necessary to compare the rate of complete resolution of symptoms between the two groups. Our study comprising two independent groups and this variable being dichotomous (resolution: yes or no), a Chi-Square test will be used. This same test will also be used to compare the response of TPM in the NESIS versus non-NESIS subgroups and the same comparison with LEV will also
be performed. Subsequently, as sub-analyses, the decrease in the frequency, intensity and duration of episodes (continuous variables) will also be compared in the two groups using a Student's T-test after validation of assumptions underlying the test.

Secondary outcome: tolerance to the antiepileptics used. To do this, we will analyze the comparison of the dropout rate (dichotomous variable: yes or no) and the side effect rate (categorical variable) using a chi-square test.

Degree of significance
We retained a significance level corresponding to an error $\alpha$ of 5%, whether a value $p<0.05$. The accepted beta error ($\beta$) is 10%, for a power of 90%.

Missing data
Patients with a large number of missing data or not including the data necessary to calculate the primary outcome will be excluded from the study. Those with some missing data that do not allow certain calculations of secondary outcomes will be kept in the study, however, the sample sizes of these analyzes will be clarified during writing.

Oversight mechanism
An independent results and dropout rate monitoring committee will not be necessary. However, monitoring will be carried out by the project team.

Safety monitoring: Every month, from the time when 10 patients have been recruited, safety data (dropout, major side effects (requiring discontinuation of treatment) and persistence of neurological symptoms (yes or no)) will be compared in both groups. If a difference of more than 50% is identified for any of these data, the ethics committee will immediately be informed. A modification or discontinuation of the study will then be evaluated for reasons of safety, theoretical efficacy or futility.

Limitations of the study
Obviously, our study includes several sources of bias that we anticipate, however we will try to limit their impacts.

Selection bias
The patients who will be selected in our study may not represent the target population of our study. Indeed, a bias of voluntarism is inherent in the estimate of our study. Patients agreeing to participate in a study often do not have the same characteristics as those refusing, causing a gap between the study population and the target population. To limit the impact of this bias, we have designed our study so that it does not represent additional displacement or test for patients, in order to limit refusals to participate. In
addition, the use of a non-probability sample can lead to a reference bias. Patients attending the coordinating center may differ from those attending another, for environmental, geographic or other reasons. To limit this bias, by using a multicenter study, we took several centers that are geographically distant, which will represent the general population more fairly. In addition, the recruitment being done in a similar way for the two groups and the matching according to the home hospitals will allow to balance these possible differences which could interfere during the recruitment.

**Measurement bias**
Some fluctuation in the measuring instrument (questionnaire) may occur. In fact, over time, the patient may find the questionnaire redundant and become bored, and therefore respond less well to it. To limit the impact of this factor, we have limited the number of follow-ups. In addition, in order to balance this fluctuation in the two groups, we will use the same questionnaires in both groups.

**Compliance bias**
Because TPM causes more side effects than LEV, compliance in this group may be lower. To limit the impact of this bias, active monitoring will be carried out with patients in the event of significant side effects, in order to reduce the dose of their treatment. This will limit drop-outs, as well as encourage better compliance. Then, the antiepileptics will be introduced gradually, in order to limit the side effects which would lead to a decrease in compliance.

**Desirability bias**
Because patients will know with which antiepileptic drug they will be assigned to, they could involuntarily change their different responses during assessments. Indeed, they might be tempted to demonstrate that TPM, treatment intervention, is more effective than it actually is. The same goes for side effects, which might be exaggerated by a patient knowing to take TPM, which is known to cause more side effects. To limit this bias, with the agreement of the ethics committee, we will approach patients during consent in a non-nominal manner. Indeed, while explaining that the two treatments are as effective as each other in epilepsy, we will explain that we want to demonstrate whether there is superiority of one of the two drugs over the other. Our hypothesis considering TPM being more efficient would remain confidential especially as this remains hypothetical. In the same sense, upon consent, all possible side effects will be presented in the form of a list, not distinguishing which are found more with which antiepileptic. Thus, even knowing the antiepileptic medication prescribed, patients will not be able to influence their responses for or against a particular treatment, not knowing which characteristics belong to which treatment. The two groups will therefore have the same potential information regarding their antiepileptic drug.
Other limitations:
The effect of Levetiracetam on cortical depolarizations remains conflicting, however, if present, it may lessen the impact of our results. In addition, the favorable natural course of cortical depolarizations could mask the significant difference between our two groups.

Time and personnel management
Initial and follow-up in-clinic assessments will be performed during regular hospital hours. Telephone assessments will be carried out during the day or evening by a member of the research team.

Ethics
Consent
Before signing the consent form, patients will be informed about the subject and purpose of the study. There will also be an explanation of the antiepileptics used. A list of common and serious side effects of the two treatments will be provided and explained. This list will not indicate which side effect is attributed to which antiepileptic drug, in order to limit the desirability bias (see desirability bias above). The consent must meet the same criteria as usual; the patient must be able to offer free and informed consent. Substituted consent in the event of incapacity, with the most significant relative, at the bedside or by phone will also be authorized. Patients will be clearly informed, verbally and in writing, that participation in the study is voluntary and that they can withdraw at any time during the study. We will also explain that termination of participation in the study will not limit the treatment of their condition and medical monitoring will be provided.

Confidentiality
The confidentiality of personal information and patient results will be ensured throughout the study. Indeed, during the randomization, a random number will be provided to each patient. A file indicating these identification numbers associated with the names of the patients and their contact information will be designed separately from the data collection file. These two documents will be kept separately in the research nurse’s office. They will stay at the CHUS at all times.

By agreeing to participate in the study, patients agree that research staff have access to their medical records during recruitment and then subsequently as needed. Eventually, the results of the study will be published in a medical journal, ensuring patient confidentiality.

Risks of participating in the study
The two drugs used in the study carry certain risks and side effects. Levetiracetam can cause depression or psychosis. These effects may rarely be severe but are reversible. In addition, it is important to understand that this drug would likely be the one proposed without this study, being the best tolerated and easiest to use of all antiepileptics. This risk would therefore be the same, with or without the study. As for Topiramate, it mainly
causes gastrointestinal side effects. These are relatively frequent, but reversible and mainly lead to stopping the drug. Its use is therefore less in usual clinic, because compliance is more difficult to obtain. Thus, by participating in the study, some patients may experience these side effects and have to stop this medication, causing some loss in follow-up. They can stop the medicine without prejudice at any time during the study.

Finally, the insertion of an ECoG electrode is associated with a minimal, but higher risk of postoperative infection (1%). Continuous monitoring for a maximum of 72 hours will also require the patient to remain connected to the devices in their room during this period. ECoG is not expected to increase the length of hospital stay, as the protocol is designed to respect the usual recovery of patients following cSDH drainage.

**Anticipated impact**
We believe that the results of this project, negative or not, will be of great importance. Indeed, this study being the first on the subject and the pathology in question being frequent, our intervention could offer a new treatment for patients with cSDH and TNS not responding to the usual treatments but could also interest other researchers. TNS have a major impact on lives of patients. For example, as long as there is a suspicion of epilepsy, a patient loses his driver’s license for 6 months after each neurological episode. This can have a significant impact on the life of a patient, but also for society. So, now that we know from our preliminary study that there is possibly an effective treatment for this condition, it is our duty to test this hypothesis.

**Dissemination of results**
We plan to publish our results in a scientific journal, whether negative or positive. We would also like to present them at neurology and neurosurgery congresses. The target audience therefore represents people working in research, neurology and neurosurgery.

**Timeline**

<table>
<thead>
<tr>
<th>Date</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/2020</td>
<td>Submission of the protocol to the ethics and research committee</td>
</tr>
<tr>
<td>08/2020</td>
<td>Final approval of the research protocol</td>
</tr>
<tr>
<td>09/2020</td>
<td>Final agreements on the participation of other participating centers</td>
</tr>
<tr>
<td>10/2020</td>
<td>Hiring of the research nurse</td>
</tr>
<tr>
<td>10/2020</td>
<td>Start of randomization</td>
</tr>
<tr>
<td>10/2022</td>
<td>End of randomization</td>
</tr>
<tr>
<td>12/2022</td>
<td>End of writing and submission</td>
</tr>
</tbody>
</table>
Budget
- There will be no cost for antiepileptics, which will be prescribed and obtained from the patients’ respective community pharmacies.
- There will be no charge for administration of questionnaires, these being done in the context of the patient’s clinical follow-up. Since there is no additional follow-up than what would be expected without our study, there will be no additional office costs.
- There will be no financial compensation for patients, as no additional follow-up will be required of them.
- ECoG electrodes will need to be purchased. We anticipate that approximately 25% of patients will present TNS preoperatively and that 50% of these will accept monitoring, thus totaling 6-10 patients out of 60.

Table 6 - Budget

<table>
<thead>
<tr>
<th>Expenses</th>
<th>Cost by patient</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research nurse (35$/hour)</td>
<td>Initial meeting of 1h30 for 60 patients</td>
<td>3150$</td>
</tr>
<tr>
<td>(Let's assume that she will do all of the initial meetings in order to have a sufficient budget)</td>
<td>Meetings with patients refusing to participate in the study (30 min for about 60 patients)</td>
<td>1050$</td>
</tr>
<tr>
<td>Resident salary when drafting (2 months)</td>
<td>2 x 1400$</td>
<td>2800$</td>
</tr>
<tr>
<td>Statistician help (50$/hour)</td>
<td>3h x 50$</td>
<td>150$</td>
</tr>
<tr>
<td>ECoG electrodes</td>
<td>10 x 500$</td>
<td>5000$</td>
</tr>
<tr>
<td>Stationery and printing costs</td>
<td>N/A</td>
<td>120$</td>
</tr>
<tr>
<td>Diffusion costs</td>
<td>N/A</td>
<td>1500$</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>13 770$</td>
</tr>
</tbody>
</table>

The budget necessary for the realization of our study will be provided through the research funds of the project supervisor, Christian Iorio-Morin. Once the protocol is approved by the ethics committee, formal grant applications will be made to provincial and federal granting agencies, as well as to trauma, stroke or epilepsy associations. Dissemination costs will be covered by the neurology department of the CHUS.

Signatures of the researcher and supervisor
Suzie Adam
Main researcher.
Neurology department.
Université de Sherbrooke

Date : ____________________
(JJ/MM/AAAA)

Christian Iorio-Morin
Supervisor
Neurosurgery department
Université de Sherbrooke

Date : ____________________
(JJ/MM/AAAA)
References


   https://www.uptodate.com/contents/topiramate-drug-information?search=topiramate&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1#references [En ligne]

   https://www.uptodate.com/contents/levetiracetam-drug-information?search=keppra&source=panel_search_result&selectedTitle=1~82&usage_type=panel&kp_tab=drug_general&display_rank=1 [En ligne]


32. CTCAE, classification des effets secondaires,
   https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
## Appendix

### Appendix 1 – NESIS score

<table>
<thead>
<tr>
<th>NESIS</th>
<th>Valeur des points pour le calcul du score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features supporting NESIS</strong></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>+4</td>
</tr>
<tr>
<td>Duration of ≥ 5 min</td>
<td>+3</td>
</tr>
<tr>
<td><em>Dysphasia</em></td>
<td>+3</td>
</tr>
<tr>
<td>Migration</td>
<td>+1</td>
</tr>
<tr>
<td>≥ 5 episodes</td>
<td>+1</td>
</tr>
<tr>
<td>Stereotypy</td>
<td>+1</td>
</tr>
<tr>
<td><strong>Characteristics against NESIS</strong></td>
<td></td>
</tr>
<tr>
<td>Altered state of consciousness</td>
<td>-4</td>
</tr>
<tr>
<td>Clonic movements</td>
<td>-4</td>
</tr>
</tbody>
</table>

**Diagnosis of NESIS if total score ≥ 4 and no positive EEG**
Appendix 2 – Consent form

Filed as a separate document
Appendix 3 – Initial form

Initial form

...

Inclusion and exclusion criteria:

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 ans</td>
<td>Contraindications to Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>• Psychiatric history (depression, psychosis, risk of suicide)</td>
</tr>
<tr>
<td></td>
<td>• History of hypersensitivity (anaphylaxis, angioedema, skin reaction) to LEV</td>
</tr>
<tr>
<td>Transient neurological</td>
<td>Contraindications to Topiramate</td>
</tr>
<tr>
<td>symptoms</td>
<td>• History of hypersensitivity to TPM</td>
</tr>
<tr>
<td></td>
<td>• Glaucoma</td>
</tr>
<tr>
<td></td>
<td>• History of urinary lithiasis</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>Known epilepsy or seizure before current subdural hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Taking an antiepileptic</td>
</tr>
<tr>
<td></td>
<td>Intracranial pathology other than SDH</td>
</tr>
<tr>
<td></td>
<td>(subarachnoid hemorrhage, intraparenchymal hemorrhage, neoplasia)</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>Pregnancy or planning to be</td>
</tr>
<tr>
<td></td>
<td>Inability to carry out the necessary follow-ups for the study</td>
</tr>
<tr>
<td></td>
<td>Refusal of the attending physician</td>
</tr>
</tbody>
</table>

Demographic data:

<table>
<thead>
<tr>
<th>Data type</th>
<th>Answers</th>
<th>Specification types</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand (Right or left)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>Active, ceased, never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Type et quantity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Type et quantity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Adequate control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>With or without insulin Type 1 or 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auricular fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>Event types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraines</td>
<td>With or without aura Aura type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past stroke, TIA</td>
<td>Event type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past SDH</td>
<td>Location Past TNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past intracranial injury</td>
<td>Type Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past intracranial surgery</td>
<td>Indication Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet used</td>
<td>Indication Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant used</td>
<td>Indication Type</td>
<td></td>
<td></td>
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</table>

**SDH characteristics:**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Answer type</th>
<th>Answers</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDH type</td>
<td>Homogeneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laminar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Separated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trabecular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDH location</td>
<td>Droit, gauche ou bilatéral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDH cause</td>
<td>Traumatic or others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDH thickness</td>
<td>Millimeters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median line shift</td>
<td>Millimeters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Glasgow score</td>
<td>3-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drainage surgery</td>
<td>Yes/no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery location</td>
<td>Right, left or both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated subarachnoid hemorrhage</td>
<td>Yes/no</td>
<td>Location</td>
<td></td>
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</tbody>
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## TNS characteristics:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Answers</th>
<th>Specification types</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual symptoms</strong></td>
<td></td>
<td>Location, Visual loss, Flash, Light</td>
<td></td>
</tr>
<tr>
<td><strong>Speech symptoms</strong></td>
<td></td>
<td>Aphasia, Dysarthria, Mutism</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebellar symptoms</strong></td>
<td></td>
<td>Balance disorder, Nausea / vomiting, Dizziness / vertigo</td>
<td></td>
</tr>
<tr>
<td><strong>Motor symptoms</strong></td>
<td></td>
<td>Paresis / paralysis, Clonic movements, Change in tone</td>
<td></td>
</tr>
<tr>
<td><strong>Sensory symptoms</strong></td>
<td></td>
<td>Hypoaesthesia, Paresthesia</td>
<td></td>
</tr>
<tr>
<td><strong>Altered state of consciousness</strong></td>
<td></td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td></td>
<td>Seconds/minutes</td>
<td></td>
</tr>
<tr>
<td><strong>Number of episodes</strong></td>
<td></td>
<td>Per unit of time</td>
<td></td>
</tr>
<tr>
<td><strong>Symptom migration</strong></td>
<td></td>
<td>How long, From what place to what place</td>
<td></td>
</tr>
<tr>
<td><strong>Stereotypy of symptoms</strong></td>
<td></td>
<td>If not: try to distinguish the different episodes</td>
<td></td>
</tr>
<tr>
<td><strong>Prodrome</strong></td>
<td></td>
<td>How long before the episode, Type of symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Postictal</strong></td>
<td></td>
<td>Duration</td>
<td></td>
</tr>
</tbody>
</table>

### Other comments:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Appendix 4 – Follow-up form

Follow-up form

Part 1 – Neurological symptoms
Persistence of transient neurological symptoms? Yes ☐ No ☐
- If no : go to part 2.
- It is still important to validate all types of neurological symptoms with the patient in order to be sure that they are absent.

TNS characteristics :

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Answers</th>
<th>Specification types</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual symptoms</td>
<td>Location</td>
<td>Location</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual loss</td>
<td>Visual loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flash, light</td>
<td>Flash, light</td>
<td></td>
</tr>
<tr>
<td>Speech symptoms</td>
<td>Aphasia</td>
<td>Aphasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
<td>Dysarthria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutism</td>
<td>Mutism</td>
<td></td>
</tr>
<tr>
<td>Cerebellar symptoms</td>
<td>Balance disorder</td>
<td>Balance disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea / vomiting</td>
<td>Nausea / vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness / vertigo</td>
<td>Dizziness / vertigo</td>
<td></td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>Paresis / paralysis</td>
<td>Paresis / paralysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonic movements</td>
<td>Clonic movements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Change in tone</td>
<td>Change in tone</td>
<td></td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Hypoaesthesia</td>
<td>Hypoaesthesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>Paresthesia</td>
<td></td>
</tr>
<tr>
<td>Altered state of consciousness</td>
<td>Duration</td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Seconds/minutes</td>
<td>Seconds/minutes</td>
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</tr>
<tr>
<td>Number of episodes</td>
<td>Per unit of time</td>
<td>Per unit of time</td>
<td></td>
</tr>
<tr>
<td>Symptom migration</td>
<td>How long</td>
<td>How long</td>
<td></td>
</tr>
<tr>
<td></td>
<td>From what place to what place</td>
<td>From what place to what place</td>
<td></td>
</tr>
<tr>
<td>Stereotypy of symptoms</td>
<td>If not: try to distinguish the different episodes</td>
<td>If not: try to distinguish the different episodes</td>
<td></td>
</tr>
<tr>
<td>Prodrome</td>
<td>How long before the episode</td>
<td>How long before the episode</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type of symptoms</td>
<td>Type of symptoms</td>
<td></td>
</tr>
<tr>
<td>Postictal</td>
<td>Duration</td>
<td>Duration</td>
<td></td>
</tr>
</tbody>
</table>
Part 2 – Side effects

Was the antiepileptic treatment discontinued by the patient?  Yes □ No □
If yes, why?  __________________________________________________________

Has the dose already been changed during a previous follow-up?  Yes □ No □
(Do not ask for the patient's dose in order to stay blind)

Are there any missed doses?  Yes □ No □
If yes, at what frequency?  ______________________________________________

Possible side effects

<table>
<thead>
<tr>
<th>Type</th>
<th>Yes/no</th>
<th>Type</th>
<th>CTCAE grade</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite/weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure/orthostatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in behavior/irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other side effects (specify CTCAE grade):
________________________________________________________________________
________________________________________________________________________

Other comments:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
Appendix 5 – Participant notebook

Notes section

Neurological symptoms
- We are looking for transient neurological symptoms (lasting less than 60 minutes).
- To complete the table - types of neurological symptoms:
  A. **Visual symptoms**
     - Specifications:
       1. Visual loss
       2. Light flash
       3. Sparkles
       4. Other (Specify)
  B. **Sensory symptoms**
     - Specifications:
       5. Numbness
       6. Loss of sensation of the skin
       7. Other (specify)
  C. **Vertigo/dizziness**
     - Specifications:
       8. Spinning part
       9. Impression of turning on oneself
       10. Other (specify)
  D. **Nausea and vomiting**
  E. **Gait disturbances**
     - Specifications:
       11. Balance disorders such as when consuming too much alcohol
       12. Other (specify)
  F. **Motor symptoms**:
     - Specifications:
       13. Paralysis or sudden weakness
       14. Abnormal involuntary movements of a limb
       15. Other (specify)
  G. **Speech disorder**:
     - Specifications:
       16. Inability to understand others
       17. Inability to speak
       18. Inability to articulate properly
       19. Other (specify)
  H. **Loss of consciousness**
  I. **Others**
- Specify in : Other comments

<table>
<thead>
<tr>
<th>Date and time of the event</th>
<th>Type of symptoms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type of symptoms (A-B-C-D-E-F-G-H-I):</td>
<td>Duration of symptoms (seconds):</td>
</tr>
<tr>
<td></td>
<td>Specifications (See those proposed under the type of symptom) (1-2-3...):</td>
<td>Onset of symptoms:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Sudden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>☐ Gradual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other comments :</td>
</tr>
</tbody>
</table>

...  

Side effects
- Try to answer the questions in the table once every two weeks, even if no new symptoms have arisen.
- If bothersome or severe symptoms: notify a member of the research team, the dose could be adjusted or discontinued.
- List of symptoms that could occur:
  A) In general:
    1. Fatigue
    2. Dizziness
    3. High blood pressure
    4. Skin rashes
    5. Hair loss
    6. Fever
    7. Joint pain
  B) Intestinal:
    1. Weight loss
    2. Appetite loss
    3. Abdominal pain
    4. Nausea and vomiting
    5. Diarrhea
6. Gastroesophageal reflux disease

C) Urinary:
   1. Urinary infection
   2. Kidney stones

D) Neuropsychiatrics:
   1. Fatigue
   2. Anxiety
   3. Irritability
   4. Agressivity
   5. Agitation
   6. Emotional lability
   7. Psychosis
   8. Depression
   9. Memory impairment
   10. Confusion

E) Neurologics:
   1. Headaches
   2. Gait disturbance, loss of balance
   3. Numbness

F) Infectious:
   1. Sinus infection

G) Ocular:
   1. Glaucoma

H) Others:
   1. Specify

<table>
<thead>
<tr>
<th>Date</th>
<th>Symptoms description</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type of symptoms (ex: A3):</td>
<td>Intensity (mild-moderate or severe):</td>
</tr>
<tr>
<td></td>
<td>If category Others (H), please specify:</td>
<td>Frequency (rarely, sometimes, often):</td>
</tr>
</tbody>
</table>

Other comments

__________________________________________________________________________