JNI Jurnal Neuroanestesi Indonesia

Literature Review

Levetiracetam as an Alternative to Phenytoin for Prophylactic Use in Post-Traumatic Seizures: a Literature Review

Gabriela Nagatri[*)], Dicky Arjuna Situmorang[*)], Natanael Ramoti[*)], Rr. Suzy Indharty[**)], Steven Tandean[**)], Andre Marolop Pangihutan Siahaan[**)]

[*)]Faculty of Medicine, Universitas Sumatera Utara, Medan, [**)]Department of Neurosurgery, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Received: August 22, 2024; Accepted: September 24, 2024; Publish: October 24, 2024

Corresponding Author: andremarolop@usu.ac.id

Abstract

Traumatic brain injury (TBI) is a common concern for the causes of disability and mortality and it can cause post-traumatic seizure (PTS). Currently, Brain Trauma Foundation (BTF) recommends phenytoin (PHY) as early PTS prophylaxis for patients with severe TBI. The two most common drugs prescribed for PTS are levetiracetam (LEV) and PHY. However, PHY displays a wide array of disadvantages. LEV appears as a better alternative to PHY because of its easier administration, the absence of need for drug level monitoring, lower drug-drug interaction, and better side-effects profile. It is due to the linear elimination kinetics LEV had in comparison to PHY that have zero order pharmacokinetics. Theoretically, LEV is better than PHY. But according to prior studies, LEV and PHY have comparable efficacy at preventing PTS in the early stages. Furthermore, the current evidence is insufficient to definitely recommend LEV over PHY in terms of effectiveness and adverse effects. This study aimed to analyze levetiracetam as an alternative to phenytoin for prophylactic use in post-traumatic seizure.

Keywords: Levetiracetam, phenytoin, prophylaxis, post-traumatic seizure, traumatic brain injury

J. neuroanestesi Indones 2024;13(3): 167–73

I. Introduction

Traumatic brain injury (TBI) is a common concern for the causes of disability and mortality with an incidence rate of 64 to 74 millions per year.[1] One of the TBI sequelae is post-traumatic seizure (PTS), which has been found to occur between 4 to 25% of the time.[2] The protocol for PTS prevention in patients with TBI is based on guidelines from the Brain Trauma Foundation (BTF) and the American Academy of Neurology (AAN). For patients with severe TBI, BTF currently recommends phenytoin (PHY) usage for early PTS prevention.[3] Besides PHY, levetiracetam (LEV) is also the most common drug that is prescribed for PTS prophylaxis. However, while PHY is generally well tolerated, it can cause detrimental side effects, such as drug to drug interactions, hypersensitive adverse effects, and induction of the hepatic cytochrome P450 (CYP) system. Due to these concerns, LEV has gained popularity as a substitute for PHY, owing to its several advantages.[4] The purpose of this literature review is to analyze levetiracetam as an alternative to phenytoin for prophylactic use in post-traumatic seizure (PTS).

II. Method

The method s used in this study was literature review, in which researchers searched, combined, and drew conclusion from various journals. The literature source were taken from Google Scholar, Pubmed, Science Direct, Cochrane

doi: https://doi.org/10.24244/jni.v13i3.622
ISSN (Print): 2088-9674 ISSN (Online): 2460-2302

JNI is accredited as Sinta 2 Journal: https://sinta.kemdikbud.go.id/journals/profile/796

How to cite: Nagatri G, et al, "Levetiracetam As An Alternative To Phenytoin For Prophylactic Use In Post-Traumatic Seizures: A Literature Review".

Library, and etc. The keywords "levetiracetam", "phenytoin", "prophylaxis", "post traumatic seizure", and "traumatic brain injury" were used. literature relevant to the chosen topic and did not exceed 10 years of publication, except, if there was new literature that opposed the reference. Meanwhile, the exclusion criteria for this study was the research concerning use of anti epileptic drugs (AED) but did not include LEV and PHY efficacy as PTS prophylaxis. The selected journal would then be examined further according to the title and abstract of the research. Subsequently, the data obtained would be organized systematically according to the topics of this study.

III. Traumatic Brain Injury

Anatomical and functional damage to the brain caused by direct mechanical trauma from outside forces is known as TBI. With an annual incidence rate of 64 to 74 million, TBI is a prevalent cause of disability and death. In developing country, TBI is more prevalent and causes between 25% and 33% of all unintentional deaths. The most prevalent victims of TBI are men, and they are more common in those between the ages of 15 and 30. Despite being preventable, TBI continues to be a major global public health concern.[1,3,5] The Glasgow Coma Score (GCS) is often used to identify the severity of TBI: mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS < 9). Globally, most TBIs are mild, accounting for 75–90% of reported cases as determined by the GCS. TBIs are linked to multiple causes of damage, such as falls, injuries from motor vehicles or other forms of road trauma, injuries sustained in sports, and physical violence in interpersonal relationships or other forms of violence (e.g., blast injury).[1,3] It has been found that moderate to severe TBI will be more likely to cause PTS. But, it does not rule out the possibility of mild TBI to cause PTS. The incidence of PTS after mild TBI is 0.38%. Meanwhile the incidence of PTS after moderate and severe TBI is 0.8% and 0.5%. The higher incidence of PTS causes by moderate TBI than severe TBI, may resulted from much lower moderate TBI incidence than severe TBI (15.467 and 54.545).[6]

IV. Post-Traumatic Seizure

PTS is one of the consequences of TBI and has been shown to occur 4–25% of the time. PTS is mainly divided into three categories: immediate (beginning 24 hours after the injury), early (24 hours to 7 days following the injury), and late (seven days after the injury).[3,7] Severe TBI, long-term alcohol abuse, linear or depressed skull fracture, younger age (less than 65), subdural hematoma, intracerebral hemorrhage, penetrating head injury, glasgow coma scale (GCS) score <10, post-traumatic amnesia for >30 minutes, and immediate seizures are risk factors for early PTS. In addition to that, the risk factor for late PTS is, early PTS, acute intracerebral hematoma, brain contusion, loss of consciousness, post-traumatic amnesia >24 hours, and age >65 years old.[8] It seems that early PTS raises the likelihood of late PTS, which is linked to post-traumatic epilepsy (PTE), another crippling consequence that manifests at least a week following a head injury.[3] Following a TBI, PTS can disrupt cerebral tissue oxygen transport, blood pressure, and intracranial pressure, all of which can be significant sources of disability. Patients' post-TBI rates of morbidity and mortality are likewise elevated by early PTS.[7]

V. Post-Traumatic Seizure Prophylaxis

The approach of giving antiepileptic medications (AEDs) with the goal of preventing PTSs is known as seizure prophylaxis. Seizures are thought to worsen secondary damage by raising intracranial pressure, rebleeding, increasing cerebral metabolic demands, and causing cerebral oedema. These acute physiologic derangements have the potential to cause herniation and death.[2,5,9] The standard treatment for PTS prophylaxis in patients with severe TBI is to use anti-seizure medicines (ASDs) within the first seven days following an injury, according to the recommendations of the BTF and the AAN. When it is believed that the overall benefit of treatment exceeds the dangers, the guidelines suggest using phenytoin in patients with severe TBI to reduce the rate of early PTSs. According to the guidelines, routine prophylaxis with valproate or phenytoin is not advised in order to prevent late PTSs.[7,9,10]

While PHY obtained medical approval in 1953, LEV received it in 1999. The PHY used to be the medication that was most often recommended for the prevention of seizures. PHY frequently functions well in the majority of cases, but it also frequently has negative side effects and is greatly impacted by a number of other medications. Additionally, PHY has been connected to certain negative consequences that LEV does not have, such as cytochrome P450 (CYP) induction and cutaneous hypersensitivity. However, compared to PHY, LEV is a more current antiepileptic medication that has substantially less adverse effects, fewer drug-drug interactions, a simple dosing regimen, and it does not necessitate close monitoring via serial blood sampling.[3,5,7] According to prior studies, LEV and PHY have comparable efficacy at preventing PTS in the early stages. Furthermore, there is not enough data to support a recommendation for LEV over PHY in terms of effectiveness and adverse effects. Regardless of the paucity of data, LEV has become a commonly prescribed AED for PTS prophylaxis in numerous centers, despite cost and effectiveness studies showing that LEV is more costly than PHY. Other anti-seizure drugs such phenobarbital, carbamazepine, and valproate are not frequently used for PTS prophylaxis.[2,3,9]

VI. Phenytoin as the Most Common AED Used in PTS

PHY is a hydantoin derivative, with solubility in alkali hydoxides, alcohol, acetone, and acetic acid. It can be synthesized by two methods, such as from Biltz synthesis and benzoin oxidation to produce benzyl. Biltz synthesis can be achieved by adding base-catalysed urea to produce benzilic acid. Early onset PTS can be prevented by the use of AEDs. One of the AED that is mostly used worldwide for PTS prophylaxis is PHY. The loading dose for PTS prophylaxis is 15 mg/kg, administered over 150 mg/min. The maintenance dose for prophylaxis is 100 mg PO/IV, 3 times a day, with the dose for extended release is 300 mg PO once daily for people with weight <80 kg. For people that weighs 80–110 kg, the dose that is given is 150 mg PO/IV, 3 times a day, with the extended release dose is 400 mg PO once daily. For people weight >110 kg, consult to pharmacy for PHY dose.[11] PHY plays a role in the modulation of the sodium channel, and hence will play a role in nerve cell excitability. It works by stabilizing an inactivated state of sodium channel. This event will cause action potential that is produced by activated sodium channel does not happen. Although PHY has been used for decades, the specific data of PHY effect on neural sodium channel has not yet been modulated. There are also scarce sources that compare the effect of PHY to another AEDs in terms of neural sodium channel selectivity. PHY is known as non-selective sodium channel and has been found to block nearly all sodium channel subtypes: Nav1.1, Nav1.2, and Nav1.4. PHY has also been found to inhibit Nav1.5 sodium channel, in which located on breast cell. There are also some evidences that PHY play a role in overactive Nav1.6 channel and inhibit Nav1.7 channel (dose -dependent). PHY also blocks L-type calcium channels and resulted in GABA-ergic effects. It will have a potent effect on the suppression of hyper-excitatory postsynaptic action potential. PHY is also known to have an affinity for the GABA-A receptor at high concentrations.[12,13]

PHY is generally well-tolerated and can be administered intravenously. Despite its tolerability, PHY is found to stimulate the metabolism of the liver drug enzyme system.[13] PHY can cause an induction of cytochrome P450 in the liver and will cause significant drug to drug reaction. PHY also has a high frequency of detrimental side effects, such as hypersensitivity reactions, irritation of the skin, phlebitis, arrhythmias, and hypotension. Besides that, PHY has zero order pharmacokinetics (Michaelis-Menten) which means the relationship between dose and serum levels is not linear. This will cause disproportionate change between serum drug concentration and drug dose. Because of this issue, PHY will require constant laboratory monitoring and will cause inconvenience to both of the patient and hospital staff.[14] Besides phenytoin, other AEDs such as valproate and carbamazepine also have similar therapeutic profiles. The narrow therapeutic window that these AEDs have, will make serum monitoring

of these drugs significantly important. This pharmacokinetic that is owned by some of the AEDs, necessitate the need for alternative antiepileptic therapies to prevent the occurrence of PTS.[4,5]

VII. Levetiracetam as Phenytoin Alternative

LEV is a derivative of pyrrolidine that shares no structural similarities to other anticonvulsants. Generic LEV is marketed under the Keppra brand and comes in doses of 250, 500, 750, and 1000 mg. Injectable solutions, liquid oral formulations, and extended release pills available. The recommended initial dose in adults is 500 mg twice daily with dose escalation based upon tolerance and effect on individual's. The maximum dose of LEV is 1500 mg twice daily or 3000 mg of extended release formulations once daily. Typically, the side effects that LEV can cause is headache, fatigue, weakness, irritability, dizziness, and somnolence. Besides that, the atypical and potentially detrimental side effect of LEV is hypersensitivity responses and cognitive consequences, such as suicidal ideation and behavior.[15]

While LEV dosing for typical seizure has been documented, the standard dosing strategy that is used for PTS prophylaxis has not been yet elucidated. One study found no statistically significant increase in the cumulative incidence of early PTS by three different LEV doses.[16] The three different dosing of LEV that is used in the study is ≤1000 mg/day, 1500 mg/ day, and ≥ 2000 mg/day. The cumulative incidence in different types of dose are consecutively 2.9% in ≤1000 mg/day dose, 8.8% in 1500 mg/ day dose, and 9% in ≥ 2000 mg/day. LEV with dose ≤1000 mg/day also had the lowest incidence for early PTS, death without seizure, and in hospital mortality.

LEV has been founded to partially blocks N-type calcium currents, indicating that it may have an impact on a subclass of high-voltage-activated calcium channel that is not yet known. Additionally, LEV affects the GABA-A receptor, preventing zinc and β-carbolines from negatively allosterically modulating the receptor. It is unclear on how important this action is to the medication's clinical efficacy. At therapeutic doses, LEV also suppresses AMPA-mediated currents in cortical neurons.[17] Although no transport function has been found for SV2A yet, it is a member of the major facilitator superfamily of 12-transmembrane domain transporters. In presynaptic nerve terminals, the SV2A protein is abundantly expressed and played a role in the intricate protein interactions that govern the release and recycling of synaptic vesicles. It appears to interact with synaptotagmin, which functions as the calcium sensor in presynaptic terminals. It has been suggested that via modifying sensitivity to calcium, it regulates the likelihood of vesicle fusion with the presynaptic membrane.[17] SV2A plays a role in regulating the exocytosis of neurotransmitters-containing vesicles. Although SV2A is not necessary for synaptic transmission, mice lacking SV2A have seizures. Consequently, SV2A ligands may inhibit seizures by influencing synaptic release pathways. In fact, it has been determined that SV2 is the most likely target for LEV. The main mechanism of LEV's anti-epileptic effect is its interaction with SV2A.[18] Since it exhibits linear elimination kinetics, variations in dosage result in somewhat predictable variations in serum concentrations. LEV is not metabolized by the Cytochrome P450 (CYP) enzyme family; rather, it is removed by the kidneys and processed by non-hepatic hydrolysis. Additionally, it has little drug-drug interactions because it neither induces nor inhibits CYP enzymes.

Therefore, therapeutic drug monitoring (TDM) of LEV is often unnecessary given its linear and predictable dose-serum concentration relationship, lack of drug-drug interactions, and broad therapeutic window.[3,19] Moreover, LEV is not regarded as a multidrug transporter substrate. It is believed that the multidrug transporter proteins, through their effects on drug uptake or enhancement of drug cleaving enzyme trafficking, are accountable for modifying drug concentrations at the site of action. Pharmacoresistance is thought to be primarily caused by increased expression of multidrug transporter proteins. This may help to explain why LEV has a low risk of developing

pharmacoresistance even with daily, long-term drug use.[18] The comparison of phenytoin and levetiracetam are shown in the table below.

Table 1. Comparison of Phenytoin and Levetiracetam as Post-traumatic Seizure Prophylaxis

Phenytoin	Levetiracetam
Narrow therapeutic window	Broad therapeutic window
Induction of CYP450	Neither induces nor inhibits CYP450
High frequency of detrimental side effects	Atypical and potentially detrimental side effects
Non-linear and unpredictable dose-serum concentration relationship	Linear and predictable dose-serum concentration relationship

VIII. Post-Traumatic Seizure Prophylaxis Drugs Choices

Levetiracetam usage as PTS prophylaxis has been shown to be superior compared to others. Early PTS prophylaxis with levetiracetam can be given for 7 days.[2] While prophylactic treatment of PTS is not usually recommended after one week of head injury, preventive treatment using AEDs can be helpful to reduce its incidence. Among AEDs for PTS, phenytoin has undergone the most extensive testing. For the preventative treatment of early PTS (those that develop during the first week following injury), phenytoin is helpful. However, the use of phenytoin for late PTS incidence is not supported because there is no protective benefit beyond the early PTS phase. When selecting this medication, it is crucial to be aware that phenytoin exhibits significant drug-drug interactions, has a complex side-effect profile, and necessitates monitoring of serum drug levels. Carbamazepine has a wide range of drug interactions and necessitates monitoring serum drug levels. The more recent generation of AEDs, levetiracetam, has a number of benefits over the more established ones.[20] Compared to phenytoin, levetiracetam has been found to have no significant differences for reducing late seizure after TBI (OR: 0.85), mortality (OR: 1.11), length of stay in hospital, and fewer side effects (OR: 0.69). But, it has been found that levetiracetam shortened length of stay in ICU. But this study has yet to be confirmed with high-quality randomized controlled trial (RCT) to make definite recommendation before making clinical decision.[3] The similar result has been found on several studies in which it stated that levetiracetam and phenytoin has similar efficacy or slightly superior in reducing PTS incidence, with the incidence as much as 10%.[4,5,9] Based on the study by Fordington and Manford, while levetiracetam is superior to other AEDs, in some circumstances other AEDs can be used.[6] For example, in patients with mood or behavioral problems, the first choice for prophylaxis is lamotrigine, carbamazepine, oxcarbazepine, and lacosamide. But some adverse effects of this drug still need to be issued, such as headache and sleep disturbance in lamotrigine usage, hyponatremia in carbamazepine or oxcarbazepine usage, and irritability in levetiracetam usage.

While medical treatment can be used as PTS prophylaxis, PTS is known to be refractory. As much as 30% of epilepsy is bound to have the next occurrence. In this type of issue, surgery can be considered or vagus nerve stimulation. Patients with dissociative seizure have also been found to show a lack of response to AEDs and can worsen its outcome.[6] While it is stated that levetiracetam

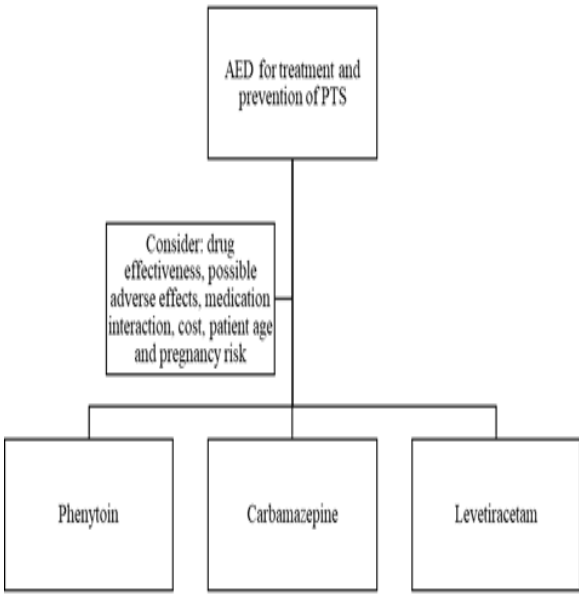

Figure 1. Post-traumatic Seizure Prophylaxis Drugs Choices

has similar efficacy as phenytoin, levetiracetam has been found to have more clinical outcome. Better safety profile, wider therapeutic index, and better cost effectiveness for levetiracetam compared to phenytoin.[9,13,14] Levetiracetam has also been found to have a lower profile of side effects and medication interactions. Neither a loading dosage nor regular serum monitoring are necessary.[20] Phenytoin has been associated with DRESS syndrome and cerebellar atrophy and higher cost (11.525 vs 10.044 dollar).[9,13] Meanwhile, levetiracetam usage will need closer monitoring in patients with renal failure or with co-administration of glucoronidation-inducing drugs. While on numerous studies levetiracetam is stated to be better in many aspects than phenytoin, but at present, levetiracetam usage has not yet been approved. So, further study should be made to confirm levetiracetam as the major first line drug for PTS.[18,19]

IX. Conclusion

Levetiracetam is associated with lower, fewer side effects, and does not require drug monitoring compared to phenytoin. This is due to linear elimination kinetics and the metabolism of this drug by kidneys. Theoretically, LEV should be more superior than PHY. However, the superiority of levetiracetam compared to phenytoin is still unclear because of the numerous studies that stated the similar efficacy of both drugs. The incidence of side effects from both drugs had also been found to not significantly different. Hence, a larger study trial that compares levetiracetam and phenytoin still needs to be done to compare both of these AEDs efficacy, side effects, and clinical outcomes as prophylaxis for PTS in TBI patients.

References

1. Haarbauer-Krupa J, Pugh MJ, Prager EM, Harmon N, Wolfe J, Yaffe K. Epidemiology of chronic effects of traumatic brain injury. J Neurotrauma. 2021;38(23):3235–47.

2. Amin TA, Nerenberg SF, Elsawy OA, Wang A, Johnston JP. Evaluation of levetiracetam for early post-traumatic seizure prophylaxis: A level II trauma center experience. Surgeon. 2023;21(2):e78–82.

3. Karamian A, Farzaneh H, Taheri M, Seifi A. Effectiveness of Levetiracetam versus phenytoin in preventing seizure in traumatic brain injury patients: A systematic review and meta-analysis. Clin Neurol Neurosurg [Internet]. 2024;240(March):108251. Available from: https://doi.org/10.1016/j.clineuro.2024.108251

4. Mengi T, Yılmaz B, Koca U, Gökmen AN. Phenytoin versus levetiracetam for posttraumatic seizure prophylaxis. Turkish J Intensive Care. 2022;20(4):201–6.

5. Ali A, Khizar A, Ahmed W, Yadav PK, Ali A, Khizar A, et al. The efficacy of Levetiracetam compared to phenytoin in prevention of post-traumatic seizures. A prospective cohort study from a low-middle-income country. Rom Neurosurg. 2023;478– 84.

6. Fordington S, Manford M. A review of seizures and epilepsy following traumatic brain injury. J Neurol [Internet]. 2020;267(10):3105–11. Available from: https://doi.org/10.1007/s00415-020-09926-w

7. Xu JC, Shen J, Shao WZ, Tang LJ, Sun YZ, Zhai XF, et al. The safety and efficacy of levetiracetam versus phenytoin for seizure prophylaxis after traumatic brain injury: A systematic review and meta-analysis. Brain Inj. 2016;30(9):1054–61.

8. Yerram S, Katyal N, Premkumar K, Nattanmai P, Newey CR. In brief. Seal Technol. 2006;1–10.

9. Candy N, Tsimiklis C, Poonnoose S, Trivedi R. The use of antiepileptic medication in early post traumatic seizure prophylaxis at a single institution. J Clin Neurosci [Internet]. 2019;69:198–205. Available from: https://doi.org/10.1016/j.jocn.2019.07.066

10. Gapp J, Tariq A, Chandra S. Acute pancreatitis. StatPearls [Internet]. 2023 Feb 9

[cited 2023 Dec 20]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK482468/

11. McGovern Medical School. Post-traumatic seizure prophylaxis in patients with traumatic brain injury clinical practice guideline. Texas: The University of Texas Health Science Center at Houston. 2024. Available from : https://med.uth.edu/surgery/ -traumaticseizure-prophylaxis-in-patients-with-traumatic-brain-injury-clinical-practice-guideline/

12. Keppel Hesselink JM. Phenytoin: a step by step insight into its multiple mechanisms of action—80 years of mechanistic studies in neuropharmacology. J Neurol. 2017;264(9):2043–7. Doi: 10.1007/s00415-017-8465-4

13. Patocka J, Wu Q, Nepovimova E, Kuca K. Phenytoin – An anti-seizure drug: Overview of its chemistry, pharmacology and toxicology. Food Chem Toxicol [Internet]. 2020;142(April):111393. Available from: https://doi.org/10.1016/j.fct.2020.111393

14. Bounthavong M, Kazerooni. Cost-effectiveness analysis of intravenous levetiracetam versus intravenous phenytoin for early onset seizure prophylaxis after neurosurgery and traumatic brain injury. Clin Outcomes Res [Internet]. 2010;15. Available from: https://doi.org/10.2147/ceor.s8965

15. Lilly LS. Pathophysiology of heart disease 6th Edition. 2016.

16. Ohman K, Kram B, Schultheis J, Sigmon J, Kaleem S, Yang Z, et al. Evaluation of levetiracetam dosing strategies for seizure prophylaxis following traumatic brain injury. Neurocrit Care [Internet]. 2023;38(2):345–55. Available from: https://doi.org/10.1007/s12028-022-01599-9

17. Sills GJ, Rogawski MA. Mechanisms of action of currently used antiseizure drugs. Neuropharmacology [Internet]. 2020;168(September 2019):107966. Available from: https://doi.org/10.1016/j.neuropharm.2020.107966

18. Deshpande LS, DeLorenzo RJ. Mechanisms of levetiracetam in the control of status epilepticus and epilepsy. Front Neurol. 2014;5(11):1–5. Doi: 10.3389/fneur.2014.00011

19. Bianchi V, Arfini C, Vidali M. Therapeutic drug monitoring of levetiracetam. Ther Drug Monit. 2014;36(5):681–5. Doi: 10.1097/FTD.0000000000000060

20. Lindberg R. Traumatic brain injury Guidelines 2022 Tele-Rehabilitation Guidelines management of seizures in the patient with traumatic brain injury. 2022. Available from: https://medicine.uams.edu/pmr/wp-content/uploads/sites/3/2022/03/Guidelines-TBI-Seizures-2022.pdf