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Review Article

# Post-Stroke Epilepsy: Current Understanding

Wei-En Johnny Tseng [a,b], Chih-Yin Lin [a], Siew-Na Lim [a], Lu-An Chen [c *]

[a] *Section of Epilepsy, Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center, and Chang Gung University College of Medicine, Taoyuan, Taiwan,* [b] *PhD Program in Biomedical Engineering, Chang Gung University, Taoyuan, Taiwan,* [c] *Department of Neurology, MacKay Memorial Hospital, Taipei, Taiwan*

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SUMMARY

Stroke is a common cause of acquired epilepsy, and nearly 50% of post-stroke epilepsy (PSE) patients are elderly. Hemorrhage has a higher incidence of post-stroke seizure (PSS) than ischemic stroke, and reports were 7% overall. PSS has different pathophysiology and is classified into early seizure, within seven days, or late seizure, which is beyond seven days after stroke. According to the latest definition, a single late PSS is qualified as structural epilepsy because of a 71.5% high risk of recurrence. Cortical involvement and early seizure are the most important risk factors for subsequent development of PSE, but no evidence supports the use of primary anti-epileptic drug (AED) prophylaxis. Statins used in the acute stage, within three days, can reduce incidence and prevent progression into chronic PSE. Comorbidity and drug-drug interactions should take into account for managing PSE, especially in the elderly population. A particular concern has raised on the increase in thrombotic events when using non-vitamin K antagonist oral anticoagulants and enzyme-inducing AEDs. Further studies on epilepsy connectome and genetic modification on synaptic plasticity, neuronal excitability should gain insight into disease-modifying treatment strategies.



## 1. Introduction

Stroke accounts for the second leading cause of death and the third leading cause of disability worldwide.[1] Hemiplegia, dysarthria, and dysphagia are common disabilities after stroke, and post-stroke seizure (PSS) is one of the most devastating sequelae. PSS may cause secondary ischemic injury and impair long-term functional outcomes.[2] Vascular disease accounts for 15% of newly diagnosed epilepsy in all age groups, and nearly 50% of post-stroke epilepsy (PSE) are elderly.[3] Patients with PSE have higher mortality rates and reduced quality of life.[4,5] With advances in stroke management such as tissue plasminogen activator and intra-arterial intervention, stroke survivors and the prevalence of PSS are expected to increase. The mainstay of treating PSE is oral anti-epileptic drug (AED) and often has a good prognosis.[6] However, up to 25% of cases are medically refractory.[7] Thus, searching for a novel treatment strategy for PSE is urgently needed. This review discusses the current understanding of the epidemiology, pathophysiology, risk factors, prediction models, and management of PSE.

## 2. Epidemiology

Post-stroke seizure incidence varies widely from 2%–20%,[8,9] and a meta-analysis, which includes both ischemic and hemorrhagic strokes, reported 7%[10] overall. This wide variability is likely due to differences in the study cohort regarding stroke etiology, study design, length of follow-up, and cutoff timeline for early and late PSS. In general, hemorrhagic stroke has a higher incidence of PSS than ischemic stroke, and the rate is about 10.6% and 8.6%, respectively.[11] Hemorrhagic stroke has a hazard ratio of 1.85, an almost twofold increase in the risk of PSS.[11] In particular, subarachnoid hemorrhage (SAH) has a higher incidence (15.2%[12]) among the hemorrhagic stroke subtypes.[8] Incidence can further be analyzed by early and late seizures. The rates were 4.3% versus 2.3% for intracranial hemorrhage[13] and 3.3% versus 1.8% (18 per 1,000 person-years) for ischemic stroke,[9] both compared in terms of early versus late seizures, respectively. Notably, the incidence of late seizure remains high during the first year and typically peaks around 6–12 months after stroke onset.[14] Early and late seizures have different underlying pathophysiology, reflecting the likelihood of developing into chronic epilepsy being higher in late PSS. The chance of seizure recurrence over the next 10 years is 71.5% after an unprovoked late PSS versus 33.0% following early PSS.[15] Thus, according to the present International League Against Epilepsy (ILAE) definition, a single late seizure after stroke qualifies as structural epilepsy because of the high (> 60%) risk of recurrence within the next 10 years.[16]

## 3. Pathophysiology

Post-stroke seizure is presumed to have a different pathogenesis and is classified into early and late seizures according to the ILAE definition.[16,17] Early PSS are seizures occurring within seven

* Corresponding author. Department of Neurology, MacKay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei City 10449, Taiwan.
*E-mail address:* 8801097@gmail.com (L.-A. Chen)

days of onset of stroke, whereas those beyond seven days are defined as late PSS or equivalent to PSE.[6,16] Acute symptomatic seizure is also considered as within the first seven days of cerebrovascular disease.[17] There are multiple aspects of ongoing process leading from stroke to epilepsy, such as neuronal excitotoxicity in early seizure, and further synaptic plasticity, reorganization in late seizure.[18] Early seizures are thought to result from the direct effect of brain hypoxia, which causes local cellular biochemical dysfunction leading to electrically irritable tissue.[19] Disruption of blood-brain barrier can activate transforming growth factor beta (TGFβ), results in increased extracellular glutamate.[18] Glutamate is a major excitotoxic neurotransmitter, which causes hyperexcitability of neurons and inappropriately activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors.[18] Maintained homeostatic equilibrium of sodium, potassium, and calcium ions is necessary for neuronal function. Ion channel dysfunction can be noted within one day after stroke in the animal model.[20] Increased intracellular calcium and sodium ions may lower seizure threshold for depolarization.[19] Increased extracellular potassium causes neuronal depolarization and promotes seizure.[21] Reduced gamma-aminobutyric acid (GABA) inhibition also leads to neuronal instability and hyperexcitability.[18] In terms of hemorrhagic stroke, hemosiderin deposits would directly cause irritation of the cortex and neuron discharges abnormally.[20] Ischemia quickly leads to pyramidal dysfunction, and electroencephalographic (EEG) focal slowing is usually seen within five minutes of acute ischemia.[8]

In contrast, late seizures occur when the brain has acquired a predisposition for seizures and epileptogenesis has taken place because of gliosis, deafferentation, selective neuronal loss, apoptosis, chronic inflammation, angiogenesis, neurodegeneration, collateral synaptic sprouting, and altered synaptic plasticity.[6,14,18] These processes do not occur independently but intertwine in a complex situation to produce structural and functional changes leading to persistent epileptogenesis.[18]

## 4. Risk factors and prediction models for post-stroke epilepsy or late seizure

Seizure itself, under cerebral ischemic conditions, would increase infarction size and impair functional recovery.[22] Thus, it is important that the PSE prediction model helps physicians identify patients who are at risk for developing seizures. Several clinical factors such as cortical stroke lesion, hemorrhagic stroke, poor score in premorbid modified ranking scale (mRS), and severe score in the National Institutes of Health Stroke Scale (NIHSS) represented higher risks for early seizure.[23–25] Majority of early seizure (50%–80%) occurred during the first 24 hours.[11,26] For late seizure or PSE, there are four prediction models[27–30] from the literature, and each has its own risk factors. The post-stroke epilepsy risk scale (PoSERS)[27] is used to assess future epilepsy risk for both ischemic and hemorrhagic strokes. Owing to the different pathophysiology of epileptogenesis in ischemic and hemorrhagic strokes, the SeLECT[29] score and PSEiCARe[30] predict late seizures after ischemic stroke, and the CAVE[28] score predicts late seizures after intracerebral hemorrhage (ICH). Cortical involvement (not included in the analysis of PSEiCARe because of the study design) and early seizures are risk factors stand out to be significant that would cause late seizure and progress into epilepsy development. This is in line with the meta-analysis that both cortical involvements, early seizure have a fourfold risk of PSE, and the presence of hemorrhage has a twofold risk of PSE.[6] Early seizure has been claimed to be the most significant risk factor for PSE in the SeLECT score.[29] Table 1 summarizes the details of the four prediction models. In Table 1, SeLECT score shows the risk of late seizures within one year but it also offers risk of late seizures within five years after stroke from the lowest value (0 point) and predicts a 1.3% to the highest value (9 points) of 83%.[29] In contrast to large cortical infarction has a higher risk of PSS, lacunar stroke carries only 1% of incidence for PSS.[31] In terms of EEG utility, it has high specificity for seizure diagnosis, but the role of detecting epileptiform discharges by EEG is not predictive for the development of early or late seizures in a clinically relevant way.[27]

## 5. Management of post-stroke epilepsy

### *5.1. Anti-epileptic drug*

The timing for initiation of AED in PSS management has been controversial in recent years. The classical definition of epilepsy requires two unprovoked seizures occurring at least 24 hours apart.[32,33] This hinders AED treatment in patients with a single unprovoked seizure after a remote brain insult, such as a stroke, central nervous system infection, or trauma. However, such brain insults have a risk of a second unprovoked seizure that is comparable to the risk for further seizures after two unprovoked seizures.[15,16] Thus, the definition was revised, a single unprovoked late PSS has fulfilled the new definition of epilepsy. Clinicians should view a single unprovoked late PSS as equivalent to PSE,[6,16] and start AED treatment promptly.

PSE has temporal evolutional changes in pathophysiological conditions from early to late seizures. The best time to initiate AED treatment is undetermined. Previous treatment trials to prevent epileptogenesis after stroke in humans were unsuccessful.[34] Primary prophylactic administration of AED to prevent a seizure is not recommended for patients with stroke.[35] Some data suggest that prophylactic use of AED therapy may be associated with poorer outcomes following ICH.[36,37] Furthermore, starting an early AED treatment at the time of early seizure did not protect from later PSE development.[38] Thus, there are no currently accepted guidelines to support the prophylactic use of AED after ischemic or hemorrhage strokes,[8] either in 2016 by the American Stroke Association[35] or in 2017 by the European Stroke Organization[39] and it has no evidence that immediate, temporary primary prophylaxis with an AED can reduce mortality. Due to the high incidence of seizure recurrence after late PSS, AED treatment is usually indicated after a first spontaneous late seizure after stroke.[16]

PSE in most patients is successfully treated with monotherapy. However, there is no available recommendation on the choice of AEDs to treat PSE. A recent systemic review[40] reported on two randomized controlled trials that assessed the efficacy and tolerability of different AEDs on secondary PSE prevention. One compared lamotrigine (LTG) with controlled-release carbamazepine (CR-CBZ),[41] and the other compared levetiracetam (LEV) with CR-CBZ.[42] The efficacy comparison between LTG, LEV, or CR-CBZ did not reveal any significant difference, but LTG and LEV were better tolerated than CR-CBZ. This is consistent with the fact that LTG and LEV have higher retention rates followed by oxcarbazepine, valproic acid, carbamazepine, and phenytoin in PSE.[43] Newer AEDs are better tolerated, have fewer drug-drug interactions and better side-effect profiles.[8] There are no evidence-based guidelines for PSS,[14] and studies have not found supportive evidence that AEDs prevent or lower the risk of first stroke-related seizures.[14,35,36,39] Thus, the decision to initiate AED treatment should be individualized, primarily based on assumed efficacy, age, concurrent medications, comorbidities, and side-effect profiles.[14]

**Table 1**
Four post-stroke epilepsy prediction models.

| Prediction model | Post-stroke Epilepsy Risk Scale (PoSERS) | CAVE score | SeLECT score | PSEiCARe[b] |
|---|---|---|---|---|
| Stroke type | Ischemia and hemorrhage (exclude SAH, CVT) | ICH | Ischemia | Ischemia |
| Risk factors (values) | 1. Supratentorial stroke (2)<br>2. ICH involving cortical area (2)<br>3. Seizure occurred 15 days or later after stroke (2)<br>4. Ischemia and ongoing neurologic deficit (1)<br>5. Stroke caused neurological deficit with mRS ≥ 3 (1)<br>6. Seizure occurred up to 14 days after stroke (1)<br>7. Ischemia involving cortical or cortical-subcortical areas (1) | 1. Cortical involvement (1)<br>2. Age < 65 years (1)<br>3. Volume > 10 ml (1)<br>4. Early seizures (1) | 1. Early seizure (3)<br>2. Cortical involvement (2)<br>3. Stroke severity<br>• NIHSS ≤ 3 (0)<br>• NIHSS 4–10 (1)<br>• NIHSS ≥ 11 (2)<br>4. Large-artery atherosclerosis (1)<br>5. MCA territory (1) | 1. Seizure at stroke admission (6)<br>2. ICU stay (3)<br>3. Cognitive impairment; dementia (2)<br>4. Atrial fibrillation (2)<br>5. Prolonged hospital stay, > 2 weeks (1)<br>6. Age ≥ 80 years (1)<br>7. Pneumonia on stroke admission (1) |
| Estimation for Risk estimate | Post-stroke epilepsy<br>6 points:<br>Sensitivity 80%<br>Specificity 98.4%<br>PPV 66.6%<br>NPV 98.8%<br>7 points:<br>Sensitivity 70%<br>Specificity 100%<br>PPV 100%<br>NPV 97.3% | Late seizure<br>0 point: 0.6%<br>1 point: 3.6%<br>2 points: 9.8%<br>3 points: 34.8%<br>4 points: 46.2% | Late seizure[a]<br>0 point: 0.7%<br>1 point: 1%<br>2 points: 2%<br>3 points: 4%<br>4 points: 6%<br>5 points: 11%<br>6 Points:18%<br>7 Points:28%<br>8 Points:44%<br>9 Points:63% | 1st year post-stroke epilepsy<br>Incidence in 100 person-years (95% CI)<br>0 point: 0.64 (0.56–0.71)<br>1–5 points: 2.62 (2.43–2.82)<br>6–10 points: 10.3 (9.48–11.3)<br>≥ 11 points: 28.2 (24.0–33.0) |
| c-statistic (95% CI) | | 0.69 (0.59–0.78) | 0.77 (0.71–0.82) | 0.792 |
| Validation | No | Independent prospective ICH cohort | Three external ischemic cohorts | Independent ischemic cohort |
| Reference | 25 | 26 | 27 | 28 |

[a] Risk of late seizures within one year after stroke.
[b] PSEiCARe is a retrospective study using the National Health Insurance Research Database of Taiwan. Due to the study design, seizures at stroke admission were defined as early seizure, ICU stay, and prolonged hospital stay representing stroke severity; and cortical lesions were not included.
CI, confidence interval; CVT, cerebral venous thrombosis; ICU, intensive care unit; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage.

### *5.2. Statins*

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and have well-established efficacy in treating hyperlipidemia in the management of atherosclerotic disease.[44] Besides lowering cholesterol, statins have pleiotropic effects,[45] including improvement of endothelial function, suppression of vascular inflammation, and reduction in T-cell activation with a decrease in cytokines. Collectively, statins are thought to possess neuroprotective property[46] and not only have anti-epileptic effect in animal studies[47–49] but also exert epileptogenic modification in humans.[50–53] A recent meta-analysis showed statin use was associated with lower risks of early PSS and PSE.[54] Regardless of low-density lipoprotein cholesterol level, statin treatment can reduce incidence of PSS in ischemic stroke.[23,50,55] The key issue is early use of statin within three days may reduce the risk of early PSS[50] and prevent the progression into chronic PSE.[50,52–55] Higher post-stroke cumulative statin doses were associated with lower PSE hazards,[53] and the risk for hospitalization from seizure decreased by 5% for every 1-gram increase in atorvastatin annually.[56] However, the benefits of previous use of statins before stroke are controversial,[46] and many studies did not show reduced seizure occurrence.[50,52–55] Although evidence of statins for epilepsy prevention in ICH is scarce, lipophilic statins (simvastatin, atorvastatin, and lovastatin) were significantly associated with reduced risk of PSE, and similar trend was found in hydrophilic statins (pravastatin and rosuvastatin).[52] The possible antiepileptic mechanism of statins may be related to the reduction in neuroinflammation mediated by a decrease in pro-inflammatory cytokines and action in the nitrergic system.[57] In addition, statins were found to suppress reactive astrocytosis,[58] which ameliorate the pathophysiological change of late PSS.

### *5.3. Comorbidity and co-medication*

PSE mainly affects the elderly; hence, clinicians should consider the peculiar pharmacodynamics and pharmacokinetics of AEDs in this population, the coexistence of comorbidity, and therefore the interactions with concomitant treatments.[6] Cytochrome P450 3A4 or P-glycoprotein enzyme-inducing AEDs can reduce the efficacy of co-administered medications such as oral anticoagulants, calcium antagonists, steroids, antimicrobial, and antineoplastic drugs through induction of drug metabolism.[59] Whereas enzyme-inhibiting AED results in decreased metabolic clearance of the affected drug, the serum concentration of which may increase, leading to toxic effects.[59] For patients with PSE, first-generation AEDs such as phenytoin, phenobarbital, and benzodiazepines have been shown to alter or delay functional recovery.[60] Non-vitamin K antagonist oral anticoagulants (NOACs) have now been frequently prescribed to patients with atrial fibrillation. Concomitant use of NOACs and enzyme-inducing AEDs has raised concerns about theoretical drug interactions, potentially leading to subtherapeutic drug concentrations and treatment failure.[61,62] The clinical relevance of these drug

interactions is largely unknown, and there are only sporadic case reports in humans.[63] Despite data mainly from *in vitro* and animal studies, clinicians should be cautious when using NOACs and AEDs together.[64] At present, from a neurologist point of view, it is inappropriate to state that AED is contraindicated due to reduced NOAC plasma levels.[63] Further convincing clinical evidence is needed.

## 6. Conclusion

Stroke is a common cause of acquired epilepsy among the elderly. Identifying patients who are at risk for PSE and promptly starting treatment improve prognosis. To date, AEDs remained the mainstay treatment for stroke-related seizures and epilepsy, many of the commonly used AEDs are appropriate as long as they are selected after consideration of drug-drug interactions and side effects.[8] For those medical refractory epilepsies, neurostimulation should be a treatment option such as vagal nerve stimulation,[65] but report on the efficacy of deep brain stimulation or cortical stimulation in treating PSE has not been found in the literature. In fact, there is an unmet need for prevention strategies against epileptogenesis or recurrence of PSE. Reduced brain inflammation and cytokines, balanced glutamate and GABA neurotransmitters, and preserved ion channel functions should shed light on future treatment plan. Connectome research on epilepsy and genetic modification on synaptic plasticity, neuronal excitability, and glial scar formation opens a novel pathway to treat not only PSE but also every single patient with epilepsy.

## Conflict of interest

Authors declared no conflict of interest.

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