CRITICAL REVIEW AND INVITED COMMENTARY

Epilepsy in cerebrovascular diseases: Review of experimental and clinical data with meta-analysis of risk factors

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Summary

Objective: Seizures may occur in close temporal association with a stroke or after a variable interval. Moreover, epilepsy is often encountered in patients with leukoaraiosis. Although early post-stroke seizures have been studied extensively, less attention has been paid to post-stroke epilepsy (PSE) and to epilepsy associated with leukoaraiosis (EAL). The aim of this paper is to review data concerning pathophysiology, prognosis, and treatment of PSE and EAL.

Methods: We performed an extensive literature search to identify experimental and clinical articles on PSE and EAL. We also conducted a systematic review of risk factors for PSE and EAL among eligible studies.

Results: PSE is caused by enhanced neuronal excitability within and near the scar. The role played by white matter changes in EAL remains to be elucidated. Meta-analysis showed that cortical involvement (odds ratio [OR] 3.71, 95% confidence interval [CI] 2.34–5.90, $p < 0.001$), cerebral hemorrhage (OR 2.41, 95% CI 1.57–3.70, $p < 0.001$), and early seizures (OR 4.43, 95% CI 2.36–8.32, $p < 0.001$) are associated with an increased risk of PSE. As regards EAL, no prospective, population-based studies evaluated the role of different variables on seizure risk. Studies about the management of PSE are limited. PSE is generally well controlled by drugs. Data about risk factors, prognosis, and treatment of EAL are lacking.

Significance: Pathophysiology and risk factors are well defined for PSE but need to be elucidated for EAL. Management of PSE and EAL relies on the clinician's judgment and should be tailored on an individual basis.

KEY WORDS: Animal models, Antiepileptic drugs, Leukoaraiosis, Seizures, Stroke.

Seizures may occur at the time of or in close temporal association with stroke (acute symptomatic, provoked, situation-related, or early seizures [ES]) or after a variable interval (several days/years) following stroke (late or remote symptomatic seizures or post-stroke epilepsy; PSE). These two conditions have different pathophysiologic mechanisms: transient cellular biochemical dysfunctions for ES, and gliotic scarring with persistent changes in

Key Points

- We review data concerning pathophysiology, prognosis, and treatment of epilepsies associated with cerebrovascular diseases
- Meta-analysis showed that cortical involvement, cerebral hemorrhage, and early seizures are associated with an increased risk of post-stroke epilepsy
- Pathophysiology and risk factors for epilepsy associated with leukoaraiosis remain to be elucidated

neuronal excitability for PSE.[1] Moreover, these two conditions carry a different prognosis in terms of long-term (10 years) risk of seizure recurrence: 20% after a single ES and 60% after the first remote seizure.[2] These findings are at the basis of the new practical clinical definition of epilepsy, intended as a disease occurring even after a single unprovoked seizure if risk of recurrence within the next 10 years is at least 60%.[3] Although stroke-related ES have been extensively studied both in humans and in experimental models, less attention has been paid to PSE. This is probably due to the lack of collaboration between stroke physicians and epileptologists and led to focus on studies on clinical characteristics of strokes rather than on electroclinical features of seizures in PSE.[4] Moreover, a detailed analysis of the literature shows relevant differences in terms of definition, pathophysiology, and outcome of PSE. Seizures may also occur in patients with small vessel diseases (SVDs). SVDs have received little attention until recently, when modern brain imaging technologies allowed detecting small deep infarcts and white matter rarefaction (i.e., leukoaraiosis).[4,5] Leukoaraiosis is often observed in adult patients with otherwise unexplained new-onset epilepsy (epilepsy associated with leukoaraiosis, EAL), but its epileptogenic role is still matter of debate.[4,5] SVD is commonly caused by arteriolosclerosis or by more rare heterogeneous conditions.[5]

This paper is a comprehensive review of the literature on experimental models, epidemiology and treatment of epilepsies associated with cerebrovascular diseases, including PSE defined as remote symptomatic seizures following a stroke, and EAL defined as epilepsy associated with leukoaraiosis due to arteriolosclerosis. To identify predictors of epilepsy, we also performed a systematic review on risk factors of PSE and EAL. The aim of this review is to encourage both clinical and experimental research on this topic.

Methods

Literature review and search strategy

See Supporting information, Data S1.

Systematic review and meta-analysis for risk factors of post-stroke epilepsy and epilepsy associated with leukoaraiosis

Inclusion criteria for PSE were the following: distinction between early and late post-stroke seizures; precise stroke timing; evaluation of at least one of seven predetermined variables as potential risk factors (age, sex, cortical involvement, primary hemorrhage or hemorrhagic transformation of ischemic stroke, infarct extension or severity, treatment with intravenous tissue plasminogen activator [tPA], occurrence of ES, and treatment of ES). Exclusion criteria were the following: follow-up duration of <12 months and sample size of <50 patients. According to the practical definition of epilepsy,[3] we considered a single late post-stroke seizure as equivalent to PSE. We followed the guidelines of the International League Against Epilepsy (ILAE),[6] which define seizures occurring within the first 7 days after stroke as ES and seizures occurring afterwards as PSE. Specific sub-analyses were planned to take into account differences in time-span for defining ES, study design, and population. As for EAL, the only inclusion criterion was the evaluation of at least one of five pre- determined variables as potential risk factors (age, sex, systemic hypertension, microbleeds at magnetic resonance imaging [MRI] studies, grading of leukoaraiosis on brain computed tomography [CT] or MRI studies), and the only exclusion criterion was sample size of <50 patients.

We used odds ratios (ORs) and 95% confidence intervals (CIs) to compare proportions of incident seizures between the exposed and the nonexposed groups. Heterogeneity

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among studies was quantitatively assessed with the I^2 index (presence of heterogeneity when $I^2 \geq 50\%$). Both fixed and random-effect models were used. Meta-analysis was performed with Comprehensive Meta Analysis, version 3.3.070.

Results and Discussion

Pathophysiology: experimental and clinical data

Post-stroke epilepsy

Epileptogenesis of post-stroke scar is due to different mechanisms including changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting leading to neuronal hyperexcitability and hypersynchrony.[1] Most of the experimental data are obtained by two animal models, namely mechanical middle cerebral artery occlusion (MCAO) and photothrombosis. MCAO leads to cortico-subcortical stroke. However, this animal model develops ES but rarely PSE (Table 1).[7] In the photothrombosis model, vessel occlusion with cortical stroke is induced by injection of fresh rose bengal dye activated in the brain through an external light beam: seizures start several weeks after vessel damage but mechanisms of epileptogenesis are still controversial (Table 1).[8,9] Cortical hyperexcitability of perilesional areas after stroke has been confirmed in humans by transcranial magnetic stimulation (TMS) studies.[10] In a series of patients with stroke involving primary motor cortex, Kessler et al.[10] found a significant decrease of the TMS-induced silent period (SP) duration in either the arm or the leg on the affected side as compared to the corresponding unaffected limb in 5 of 6 PSE-patients, and in none of 76 controls without PSE. Kim et al.[11] found larger amplitude of TMS-induced motor-evoked potentials and intracortical facilitation in the affected compared to unaffected hemispheres in 18 PSE patients, but not in 18 stroke patients without epilepsy.

Epilepsy associated with leukoaraiosis

Leukoaraiosis consists of white matter rarefaction due to SVD causing small deep infarcts. White matter rarefaction and SVD are observed in spontaneous hypertensive rats (SHRs) and their stroke-prone substrain, which represent useful models to assess hypertensive brain damage and related stroke (Table 1).[12] The role of hypertension in modulating seizure susceptibility has been evaluated in different experimental studies. Accumulated evidence supports the concept that there is an independent renin-angiotensin system in the central nervous system.[13]Angiotensin peptides seem to operate through close interaction with different neurotransmitter systems including gamma-aminobutyric acid and adenosine.[13] Tchekalarova et al.[14] found that SHRs exhibited higher susceptibility than control rats to kainate-induced status epilepticus, and that losartan (an AT1 receptor antagonist) delayed the onset of kainate-induced seizures in SHRs but not in control rats. Of interest, upregulation of AT1 and AT2 receptors has been found in hippocampus of patients who underwent anteromesial temporal lobectomy for seizure control, suggesting the renin-angiotensin system participation in the pathophysiologic mechanisms of underlying epileptogenesis in these patients.[15] A few clinical studies evaluated the role of systemic hypertension as independent risk factor for seizures. In a case–control study including 521 subjects (227 patients with first unprovoked seizures and 294 controls) Ng et al.[16] found that history of hypertension is an independent risk factor (OR = 1.57) for new-onset unprovoked seizures. In a population-based case–control study including 145 incident cases of first unprovoked seizure and 290 controls, Hesdorffer et al.[17] found that severe

Table 1. Main findings in experimental models of PSE and EAL

Experimental model	Outcome	Specific findings	Translational relevance
MCAO	Low or absent ability to induce PSE (1 of 26 rats)	Gliosis in penumbral tissue	Large ischemic stroke of middle cerebral artery. Suitable model for ES. Poor relevance for PSE
Photothrombosis	Seizures start several weeks after photothrombosis (ipsilaterally to the ischemic area)	Mossy fiber sprouting in the hippocampus Altered expression of cortical $GABA_A$ receptor alpha1 subunits Hyperexcitability of thalamocortical neurons	Small cortical ischemic stroke. Poor relevance for ES. Suitable model for PSE
SHRs SHRs-SP	Increased susceptibility to developed seizures induced by kainate or selective amygdala kindling	Slower turnover rate of norepinephrine in brain stem and cortex and of dopamine in striatum RAS overactivity in anterior hypothalamic area Losartan delayed seizures onset after kainate injection Losartan did not prevent or delay seizures onset after kindling	SVD with lacunar infarcts. Suitable models for EAL

ES, early seizures; GABA, γ-aminobutyric acid; MCAO, middle cerebral artery occlusion; PSE, post-stroke epilepsy; RAS, renin-angiotensin system; SHRs, spontaneous hypertensive rats; SHRs-SP, spontaneous hypertensive rats-stroke prone; SVD, small vessel disease.

uncontrolled hypertension was associated with an 11-fold increased risk of unprovoked seizure. Hypertension (estimated through left ventricular hypertrophy) as an independent risk factor (OR 2.9) for epilepsy was found in a cross-sectional, case–control study by Li et al.[18] including 4,944 subjects (65 of whom had epilepsy). However, this study was based on prevalent cases, thus limiting the inference on the pathogenic role of hypertension in these 65 patients. A few clinical studies evaluated the relationship between leukoaraiosis, SVD, and epilepsy. Maxwell et al.[19] retrospectively evaluated 105 patients with late-onset epilepsy in comparison with 105 controls. They found that cerebrovascular disease, including severe SVD, was significantly more prevalent in patients with late-onset epilepsy than controls. However, about half of the patients included in these two studies did not undergo brain MRI, thus limiting the possibility to generalize the results. Okroglic et al.[20] retrospectively studied clinical symptoms and cerebrovascular risk factors in a cohort of 223 consecutive patients with SVD, and found that about 20% of patients presented with "stroke symptoms and seizures," especially in the presence of a high lesion load in frontal and occipitoparietal lobes. The authors speculate that some subcortical white matter lesions may also affect U-fibers, leading to a higher propensity for seizures. De Reuck and Van Maele[21] investigated the amount of cognitive decline in 292 patients with leukoaraiosis, with and without seizures (n = 44 and 248, respectively), and found a higher proportion and severity of cognitive decline in patients with seizures. These authors speculated that an underlying neurodegenerative disease, rather than leukoaraiosis, might cause epilepsy in those patients. Gasparini et al.[4] analyzed the anatomical-electroclinical correlations of patients diagnosed with PSE as compared to patients with EAL. This study included 117 patients (58 with PSE, 59 with EAL). All patients had undergone brain MRI. These two groups significantly differed in terms of seizure-onset localization: whereas in PSE patients the epileptogenic focus was coherent with the vascular lesions (see below), in EAL-patients temporal lobe epilepsy predominated. However, the possibility of a mere incidental relationship between the two phenomena (epilepsy and leukoaraiosis) should be considered, since leukoaraiosis is a common finding in the age group studied (advanced adulthood, mean age: 66.3 years) and temporal lobe epilepsy is the most frequent focal epilepsy at all ages. Therefore, it is still unclear whether leukoaraiosis can be considered as a cause of epilepsy, and the role of different variables, that is, cortical microinfarcts, needs to be elucidated. Because of very small size (<1 mm), most cortical microinfarcts are below the lower limit of spatial resolution (about 1 mm) for 1.5 T or 3 T MRI currently used in clinical practice.[22] The use of higher field (7 T) MRI may be a promising method to visualize sub-millimetric microinfarcts and to understand their role in EAL.

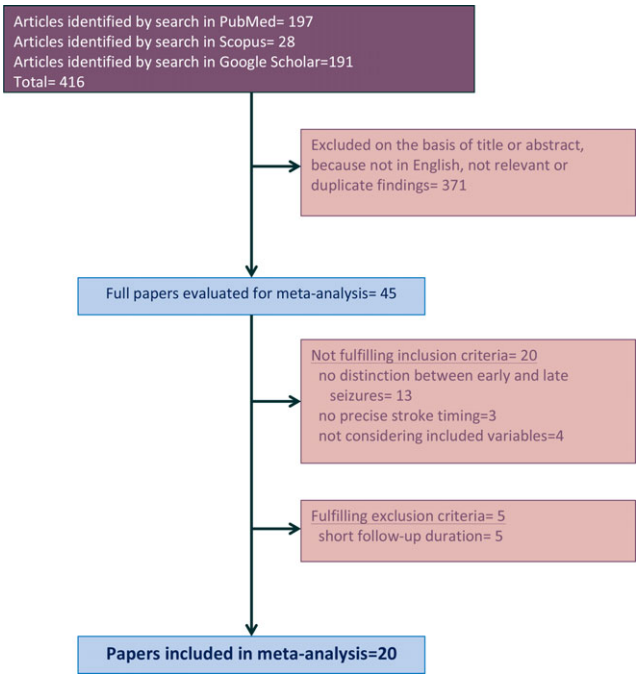

Figure 1.
Flowchart showing inclusion and exclusion criteria of studies evaluated for meta-analysis of risk factors for PSE.
Epilepsia © ILAE

Systematic review and meta-analysis of risk factors for PSE

PubMed search retrieved 197 results, Scopus search retrieved 28 results, and Google Scholar retrieved 191 results. Of those, 371 were excluded on the basis of the title/abstract or as duplicate findings, 20 did not fulfill inclusion criteria, and 5 fulfilled exclusion criteria (Fig. 1). One additional paper was selected by searching references of original articles. Thus, the meta-analysis was based on 21 studies (Table 2) (for references, see Data S2) evaluating 21,548 stroke patients. Of these, 1,411 had PSE corresponding to a global prevalence of 4.7% in cohort studies (Table 2). Included papers differed in study design, history of seizures, population, and time-span defining ES (Table 2). The diagnosis of stroke was made on the basis of clinical findings and brain imaging (CT or MRI) in all studies. Because age and infarct extension or severity were not reported in a consistent way across studies, meta-analysis could be performed on four variables (sex, cortical involvement, hemorrhage, and ES).

Analysis on cortical involvement

Six studies were included in this analysis. I^2 value was 0. Results are shown in Figure 2; cortical involvement was a predictor of PSE, bearing an almost fourfold risk of epilepsy (OR 3.71, 95% CI 2.34–5.90, $p < 0.001$). Sub-analyses confirmed that cortical involvement was a predictor of PSE (Table S1).

Analysis on hemorrhagic component

Fifteen studies were included in this analysis. I^2 value was 84%. Results are shown in Figure 3. Presence of hemorrhage was a predictor of PSE, with a twofold risk of seizures (OR 2.41, 95% CI 1.57–3.69, $p < 0.001$). Sub-analyses confirmed that hemorrhage was a predictor of PSE, with two exceptions (Table S2). Indeed, when considering only retrospective cohort studies or case–control studies, the association between hemorrhage and PSE was not statistically significant (OR 2.04, 95% CI 0.84–4.9, $p = 0.12$ for retrospective cohort studies; odds ratio 6.55, 95%CI 0.89–48.3, $p = 0.07$ for case–control studies; Table S2).

Analysis on occurrence of early seizures

Two studies were included in this analysis. I^2 value was 0. Results are shown in Figure 4; ES were a predictor, bearing a fourfold risk of PSE (OR 4.43, 95% CI 2.36–8.32, $p < 0.001$).

Analysis on sex

Thirteen studies were included in this analysis. I^2 value was 16%. Results are shown in Figure S1; sex was not a predictor of PSE (OR 0.943 for female sex, 95% CI 0.79–1.13, $p = 0.52$). Sub-analyses confirmed that sex was not a predictor of PSE (Table S3).

Variables not included in meta-analysis

The extreme variability in measurements of age (continuous variable in some studies, discrete variable with different cut-offs in other studies) and of size or severity of strokes prevented the use of these variables in the meta-analysis. Age was evaluated in 12 of 20 studies and younger age was associated with increased risk of PSE in 3 of these 12 studies (Table 2). Size or severity of stroke was evaluated in 12/20 studies and were associated with increased risk of PSE in 9 of these 12 studies (Table 2). Intravenous treatment with tPA was evaluated in a single study.[23] The authors found that PSE was more frequent among patients treated with thrombolysis compared to standard medical therapy (20.6 vs. 10.7%, $p = 0.02$), but the effect was lost in multivariate analysis.

Similarly, a single study evaluated the effects of early seizure treatment on PSE development.[24] In that study, starting an early antiepileptic treatment did not protect from later seizures (adjusted p at multivariable analysis = 0.170).

Limits, main findings, novelty

Even with limitations due to the fairly poor quality of the included studies (about half of the studies were retrospective or did not use brain MRI), our meta-analysis indicates that cortical involvement, hemorrhage, and ES are associated with a higher risk of PSE; gender was not a predictor for PSE. Data about the effect of intravenous tPA administration or of treatment of ES on development of PSE were insufficient. In the only published meta-analysis on PSE,[25] hemorrhage was not significantly associated with PSE. However, this meta-analysis[25] excluded studies on children and included four studies that did not clearly distinguish between ES and PSE; finally, it is unclear how differences in the definition of ES were treated.

Systematic review of risk factors for EAL

PubMed search retrieved 85 results, Scopus search retrieved 6 results and Google Scholar search retrieved no results. Of 91 results, 90 were excluded because they were not pertinent and one for a small sample size. Only one retrospective cohort study evaluated risk factors for epileptic seizures in patients with leukoaraiosis.[26] This study included 242 subjects with previous lacunar stroke with or without leukoaraiosis; of these, 37 had seizures. Sex, systemic hypertension, and severity of white matter changes were not associated with an increased risk of seizures. Moreover, the authors found no differences in other vascular risk factors, distribution and frequency of the lacunes, and outcome between the two groups. They concluded that there was no evidence that seizures were directly induced by lacunar infarcts and hypothesized that the occurrence of seizures in subcortical strokes could be explained by indirect or subtle cortical involvement. Of note, MRI was performed in about 50% of subjects; therefore, the number of vascular lesions could be underestimated. Moreover, this study was conducted in a selected population (patients admitted to hospital with clinical complaints in keeping with lacunar stroke) and grading of leukoaraiosis was not reliable.

To date, evidence of risk factors for EAL are insufficient. The role of hypertension and other possible determinants of epilepsy in patients with SVD need to be further evaluated.

Prognosis and treatment of PSE and EAL

General considerations

PSE mainly affects the elderly; hence, physicians should consider the peculiar pharmacodynamics and pharmacokinetics of antiepileptic drugs (AEDs) in this population, as well as the coexistence of different pathologies and, therefore, interactions with concomitant treatments. Moreover, the elderly are more vulnerable to the adverse effects of drugs and the titration of the AEDs must take into account their narrow therapeutic range ("start slow and go slow").[27] In general, PSE has a good prognosis, being well controlled by AEDs. Indeed, an observational study by Semah et al.[28] evaluated seizure frequency during 1–7 years in a cohort of 1,148 outpatients with focal epilepsy and MRI evidence of brain abnormalities. These authors found that the 36 patients with PSE had the best prognosis, 54% being seizure free. Moreover, in a prospective study by Stephen et al.[29] evaluating 550 patients with focal epilepsy aged 16 years or

Table 2. Characteristics of studies included in the meta-analysis on PSE

Study	Prevalence of PSE, %	Stroke type	Study design	Population/ No. of included subjects	Pre-existing epilepsy excluded	Acute/remote seizures cut off				Main predictors of PSE							
						<48 h	≤1 week (ILAE-defined ES)	2–4 weeks	Un specified	Cortical involvement	Extension/ Severity	Hemor-rhage	Female gender	Early seizures	Treatment of early seizures	Younger age	Intra-venous tPA
Olsen et al. (1987)[41]	9	Ischemic and hemorrhagic	P	A/77	Yes				x	+	NE	NE	0	NE	NE	NE	NE
Sung et al. (1989)[42]	4.6	Hemorrhagic	R	A/1,402	No			x		+	0	NA	NE	NE	NE	NE	NE
Kotila and Waltimo (1992)[43]	17	All types	R	A/200	No			x		0	NE	+	+	NE	NE	NE	NE
Heuts-Van Raak et al. (1996)[44]	13	Ischemic	P	A/322	No			x		NE	+	0	0	NE	NE	0	NE
Burn et al. (1997)[45]	7	All types	P	A/675	No	x				NE	+	+	NE	NE	NE	0	NE
Awada et al. (1999)[46]	NA	Ischemic	C	A/371	No			x		+	+	NA	NE	NE	NE	0	NE
Teasell et al. (1999)[47]	7.8	All types	P	A/549	Yes	x				NE	NE	+	NE	NE	NE	NE	NE
Berges et al. (2000)[48]	4.9	Unspecified	R	A/3,205	Yes			x		NE	+	0	NE	NE	NE	NE	NE
Lossius et al. (2002)[49]	2.5	All types	P	A/472	No			x		0	+	0	0	NE	NE	0	NE
Lamy et al. (2003)[50]	5.5	Ischemic	P	A/581	No		x			+	0	+	0	NE	NE	0	NE
Benbir et al. (2006)[51]	3.6	All types	P	A/1,428	Yes		x			NE	NE	+	0 (ischemic stroke)	NE	NE	NE	NE
Chen et al. (2012)[52]	NA	All types	C	A/4,126	Yes				x	NE	NE	+	NE	NE	NE	NE	NE
Elwan et al. (2012)[53]	NA	Ischemic and hemorrhagic	C	A/80	Yes			x		+	+	0	0	NE	NE	0	NE
Morais et al. (2012)[54]	29	Ischemic and hemorrhagic	R	Ch/65	Yes		x			+	NE	0	0	NE	NE	NE	NE
Graham et al. (2013)[55]	6.4	All types	P	A/3,310	Yes	x				+	+	+	0	NE	NE	+	NE
Jungehulsing et al. (2013)[56]	8.2	All types	P	A/1,020	Yes		x			NE	0	0	0	NE	NE	0	NE
Roivainen et al. (2013)[57]	10	Ischemic	R	A/978	Yes		x			+	+	+	0	+	NE	0	NE
Wang et al. (2013)[58]	11	Unspecified	R	A/2,094	Yes		x			+	NE	0	0	NE	NE	0	NE
Keller et al. (2015)[23]	14	Ischemic	R	A/302	Yes			x		+ (indirect measures)	–	NA	0	NE	NE	0	0
Kopyta et al. (2015)[59]	13	Ischemic	P	Ch/78	No		x			NE	+	NE	0	NE	NE	+	NE
Serafini et al. (2015)[24]	3.1	All types	P	A/782	No		x			+	NE	0	0	+ (hemorrhage only)	0	+	NE

A, adults; C, case–control study; Ch, children; ES, early seizures; P, cohort study, prospective; R, cohort study, retrospective; +, positive association with epilepsy; –, negative association with epilepsy; 0, no association; NE, not evaluated; NA, not applicable.
References from 41 to 59 are listed in Data S1.

older, who were treated with AEDs with a follow-up of at least 2 years, 46 (30.6%) had PSE and 31 (67%) of 46 were seizure free, most of whom (68%) were taking one AED.

Evidence supporting the administration of AEDs for primary prevention of seizures after a cerebrovascular injury is insufficient. A prospective randomized, double-blind, placebo-controlled trial by Gilad et al.[30] evaluating the efficacy of sodium valproate (VPA) in primary prevention of seizures in 72 patients with spontaneous cerebral hemorrhage followed for 1 year, showed no significant differences in terms of outcome, with PSE occurring in 16.6% of patients treated with VPA and 11.1% with placebo. No studies evaluated prognosis and treatment of EAL.

Trials comparing the efficacy of different AEDs

A few prospective studies have compared the efficacy of different AEDs in patients with PSE (Table 3). Gilad et al.[31] conducted a randomized noncontrolled trial comparing lamotrigine (LTG) and sustained-release carbamazepine (CBZ) in patients >18 years with both ES and PSE, and found that LTG was more effective, albeit nonsignificantly (seizure freedom: 72% on LTG vs. 44% on CBZ, p = 0.06), and better tolerated (withdrawal rate due to adverse events: 3% on LTG and 31% on CBZ, p = 0.02). Two prospective open-label studies evaluated levetiracetam (LEV) monotherapy in elderly patients with new-onset PSE.[32,33] Both studies reported good tolerability and efficacy profile for LEV with about 80% reaching seizure freedom. The discontinuation rate due to adverse effects (namely drowsiness) was 14–21%. In a multicenter randomized open-label trial, Consoli et al.[34] compared the efficacy of monotherapy with either LEV or sustained-release CBZ in patients with PSE. No relevant differences on seizure control were found between the two groups (94% of patients seizure free in LEV group and 85% in CBZ group, p = 0.08). However, LEV was better tolerated (31% of patients experienced side effects with LEV and 39% with CBZ, p = 0.02). Finally, in a retrospective observational study, Huang et al.[35] evaluated efficacy of phenytoin (PHT), valproate (VPA), CBZ, and new AEDs (oxcarbazepine [OXC], vigabatrin, tiagabine, LTG, TPM, gabapentin [GBP], LEV, and pregabalin) on seizure control in 3,622 patients with PSE. They found that patients treated with VPA and new AEDs have better seizure control than those using PHT, as demonstrated by the lower risks of emergency room visits and hospitalizations (Table 3).

Some other trials compared efficacy of different AEDs in patients with epilepsy due to various etiologies including cerebrovascular diseases. In a double-blind randomized trial carried out by Brodie et al.,[36] LTG and immediate-release CBZ were tested during 24 weeks in 150 patients aged ≥65 years with new-onset epilepsy. Thirty percent of patients in the LTG group and 38% in the CBZ group had a previous cerebrovascular accident. Efficacy was similar (>60% of patients reaching seizure freedom in both groups), but LTG was better tolerated as compared to CBZ, with a significantly higher retention rate at the end of the study (71% in LTG group, 42% in CBZ group, p < 0.001). Rowan et al.[37] randomized 593 epileptic patients aged 60 years or older to one of three treatment arms: LTG, immediate-release CBZ, or GBP. CBZ was less tolerated than GBP and LTG (withdrawal for adverse events: LTG 12.1%, GBP 21.6%, and CBZ 31%; p = 0.001), although the three drugs had similar efficacy, with 53.3% of patients being seizure free at 12 months (51.4% on LTG, 47.4% on GBP, 64.3% on CBZ; p = 0.09). In that study, 30% of subjects had a cerebral infarction and 16% had arteriosclerosis. The SANAD (Standard and New Antiepileptic Drugs) study[38] was an unblinded randomized controlled trial that compared (Arm A) the efficacy and tolerability of LTG, CBZ (either immediate or controlled release), GBP, TPM, and OXC in patients with new-onset focal epilepsy in different age groups. Among 1,721 enrolled, 108 (6.3%) had history of stroke. Authors found comparable efficacy between LTG and CBZ (expressed as time to treatment failure) with lesser effectiveness for GBP. LTG and TPM were, respectively,

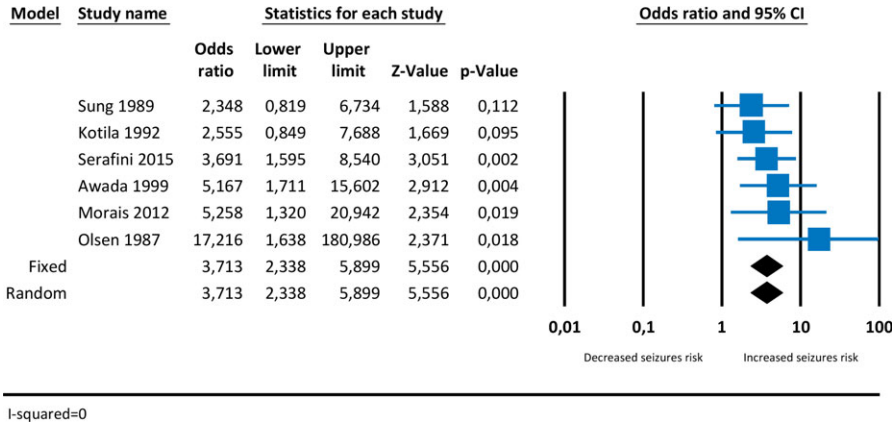

Figure 2.
Forest plot showing pooled odds ratios for cortical involvement.
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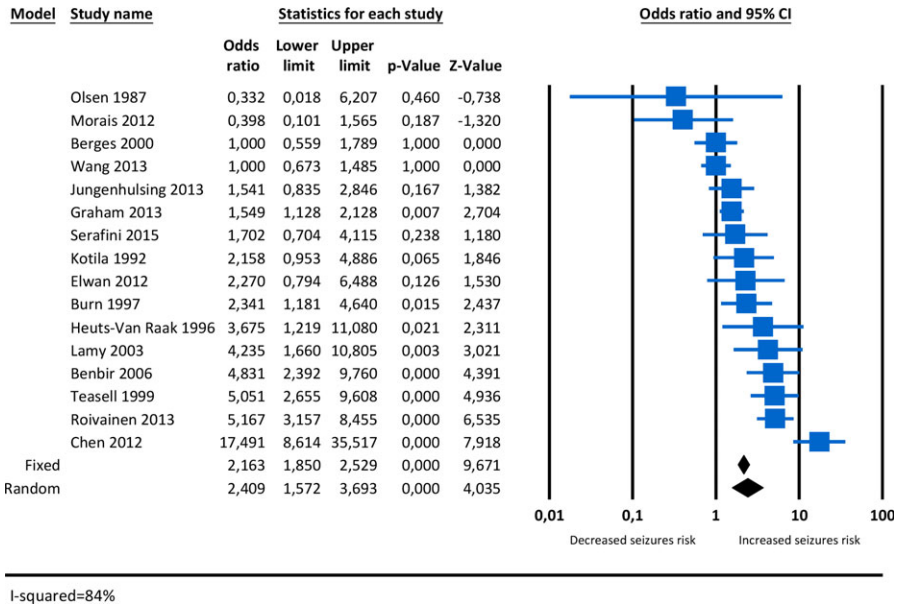

Figure 3.
Forest plot showing pooled odds ratios for cerebral hemorrhage.
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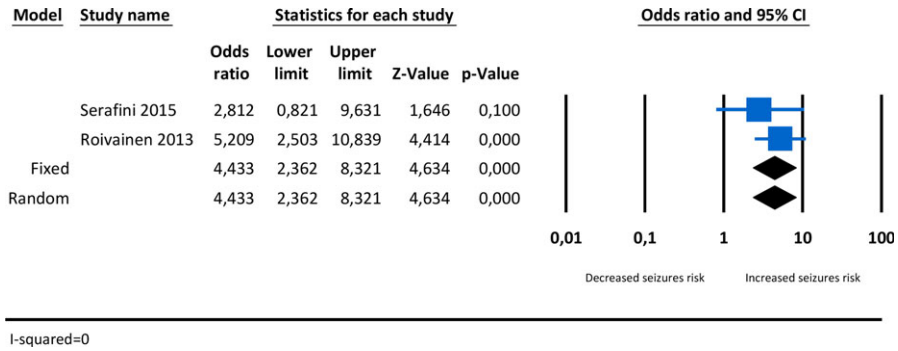

Figure 4.
Forest plot showing pooled odds ratios for early seizures.
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Table 3. Summary of the main studies evaluating antiepileptic drugs in patients with PSE

Study	Design	Evaluated AEDs	No. of included patients	Main findings
Gilad et al. (2007)[31]	Randomized, open label	LTG vs. sustained-release CBZ	64	Equal efficacy, LTG better tolerated
Kutlu et al. (2008)[32]	Uncontrolled, open label	LEV	34	Good efficacy and tolerability
Belcastro et al. (2008)[33]	Uncontrolled, open label	LEV	35	Good efficacy and tolerability
Consoli et al. (2012)[34]	Randomized, open-label	LEV vs. sustained-release CBZ	106	Equal efficacy; LEV better tolerated
Huang et al. (2015)[35]	Retrospective	PHT, VPA, CBZ, different new AEDs	3,622	VPA and new AEDs higher efficacy than PHT

AEDs, antiepileptic drugs; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; VPA, valproic acid.

the best and less-tolerated drugs (45% of patients reported adverse events while on LTG and 53% while on TPM). The limits of this study consist in its unblinded design, which might have led clinicians to biases in their therapeutic choices, and in the administration of CBZ at higher than therapeutic doses, thus obtaining more frequent side effects

with discontinuation of the drug. Moreover, the number of patients undergoing treatment with immediate release or controlled release formulation of CBZ was unspecified. Saetre et al.[39] conducted a multicenter, double-blind study on the effectiveness and tolerability of LTG and controlled release CBZ in 185 patients ≥65 years with new-onset epilepsy, most of whom had symptomatic epilepsy. Although no data on specific etiologies were reported, hypertension (42% of the randomized cohort) and cerebrovascular disease (25%) were frequent in this sample. The authors showed that the two drugs had similar profiles, with a slightly higher efficacy for CBZ (63% seizure-free patients in LTG group, 76% in CBZ group, $p = 0.07$) and a slightly better tolerability for LTG (adverse events leading to withdrawal in 14% of LTG group and 25% of subjects in CBZ group, $p = 0.08$). Finally, a randomized, double-blind trial comparing sustained-release CBZ, LTG, and LEV as the initial therapy in 359 elderly patients with new-onset focal epilepsy, most of whom had cerebrovascular lesions, found comparable efficacy among the three drugs, but the retention rate for LEV was significantly higher than for sustained-release CBZ (61.5% vs. 45.8%, $p = 0.02$), and similar to LTG (55.6%).[40]

Conclusions

Although early post-stroke seizures have been studied extensively, less attention has been paid to PSE and to EAL. Experimental models of PSE show that epileptogenesis is linked to alteration of neuronal excitability in different cortical areas, as confirmed by TMS studies in humans. The pathophysiology of EAL is largely unknown. Data from experimental and clinical studies suggest that systemic hypertension and leukoaraiosis may modulate seizure susceptibility, possibly with a contribution of cerebral renin-angiotensin system. However, coexistence of cortical microinfarcts or other adjunctive factors may also play a role. Further animal and human studies are needed to clearly define the role of risk factors, including systemic hypertension, in the development of EAL and to explain whether leukoaraiosis represents a mere incidental radiologic finding or plays a role in the pathogenesis of epilepsy. Moreover, the role of SVD and leukoaraiosis in patients with epilepsy has not yet been clarified. From the clinical point of view, our meta-analysis showed that cortical involvement, hemorrhage, and ES are associated with a higher risk PSE, whereas gender does not seem to play a role. Gender, systemic hypertension, and severity of white matter changes need to be evaluated as risk factors for EAL in prospective, population-based studies. Results from clinical studies on PSE suggest that seizure-free rate after AED treatment is high. Among AEDs, sustained-release CBZ, LTG, and LEV showed good efficacy, with a better tolerability for LTG and LEV over sustained-release CBZ. Conversely, no data are available on optimal treatment for EAL. Management PSE and EAL relies on the clinician's judgment and should be tailored on individual basis.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A Members of the Epilepsy Study Group of the Italian Neurological Society

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Forest plot showing pooled odds ratios for sex.

Table S1. Risk of PSE by stroke site (cortical vs. subcortical).

Table S2. Risk of PSE by stroke type (hemorrhage vs. infarction).

Table S3. Risk of PSE by sex (women vs. men).

Data S1. Search strategy for review.

Data S2. Studies included in meta-analysis.