The New Antiepileptic Drugs: Their Neuropharmacology and Clinical Indications

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Abstract

The administration of antiepileptic drugs (AEDs) is the first treatment of epilepsy, one of the most common neurological diseases. Therapeutic guidelines include newer AEDs as front-line drugs; monotherapy with new AEDs is delivered in Japan. While about 70% of patients obtain good seizure control by taking one to three AEDs, about 60% experience adverse effects and 33% have to change drugs. Compared to traditional AEDs, the prolonged administration of new AEDs elicits fewer adverse effects and fewer drug interactions and their teratogenicity may be lower. These characteristics increase drug compliance and allow combination therapy for drug-resistant epilepsy, although the antiepileptic effects of the new AEDs are not greater than of traditional AEDs. Comorbidities are not rare in epileptics; many adult patients present with stroke and brain tumors. In stroke patients requiring risk control and in chemotherapy-treated brain tumor patients, their fewer drug interactions render the new AEDs advantageous. Also, new AEDs offer favorable side benefits for concurrent diseases and conditions. Patients with stroke and traumatic brain injury often present with psychiatric/behavioral symptoms and cognitive impairment and some new AEDs alleviate such symptoms. This review presents an outline of the new AEDs used to treat adult patients based on the pharmacological activity of the drugs and discusses possible clinical indications from the perspective of underlying causative diseases and comorbidities.

Key words: adverse effect, side benefit, primary disease, comorbidity, neurosurgery

Introduction

Epilepsy is one of the most common neurological diseases; its first-line treatment is the administration of antiepileptic drugs (AEDs). These are divided into first-, second-, and third-generation AEDs.[1] The commonly used first-generation AEDs are phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA), zonisamide (ZNS), and clobazam (CLB). In North America and Europe, ZNS is considered as a second-generation drug. The third-generation drug includes lacosamide (LCM) and eslicarbazepine acetate; others recently delivered are included in the second generation. Post-second-generation AEDs are commonly known as new AEDs. In Japan, their administration as add-on therapy was approved in 2006 and gabapentin (GBP), topiramate (TPM), lamotrigine (LTG), levetiracetam (LEV), and rufinamide (RFN) are distributed as oral drugs. Vigabatrin (VGB), oxcarbazepine (OXC), perampanel (PER), and LCM are being considered

for approval by the Japanese Ministry of Health, Labour, and Welfare. While therapeutic guidelines have long advocated the administration of CBZ and VPA as a first drug for focal and generalized seizures,[2] based on expert opinion and recent guidelines, several new AEDs are recommended as first- and second-line drugs in patients with focal and generalized seizures.[2,3] Monotherapy with LTG and LEV is approved in Japan.

In the definition of epilepsy revised in 2014 by the International League Against Epilepsy, the condition was defined as a disease of the brain manifesting any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure with the probability of further seizures similar to the general recurrence risk of at least 60% after two unprovoked seizures occurring over the next 10 years; and (3) a diagnosis of an epilepsy syndrome.[4] Using these criteria, about 70% of patients obtained good seizure control by taking one to three AEDs.[5] However, adverse effects were experienced by about 60%, and about 4% of

patients stopped taking the drugs.[6] While the new AEDs are not superior to traditional AEDs in terms of their antiepileptic- and acute adverse effects,[7–9] their prolonged administration elicited fewer adverse effects and milder interactions with other drugs than did traditional AEDs.[10–13] Most new AEDs involve less teratogenicity and their effect on the patients' physical status, including hormone secretion and the bone and lipid metabolism, are milder.[14] The lower teratogenicity of LTG and LEV has raised interest in these drugs. The new AEDs also offer favorable side benefits with respect to concurrent diseases and conditions.[15] Several new AEDs have unique binding sites, LEV binds to synaptic vesicle 2 (SV2), PER to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and LCM to collapsin response mediator protein-2 (CRMP2). The possibility that their unique profiles render the new AEDs advantageous for combination therapy has been suggested.[11]

As it is expected that new AEDs will be prescribed widely, cognizance of their basic mechanisms of action and their specific characteristics is important. This review presents an outline for the use of these drugs in adult epileptics based on the pharmacological activity of the new generation of AEDs, and discusses clinical indications for the use of these new drugs.

Pharmacological Mechanisms of the New AEDs

Most AEDs exert their antiepileptic effects via the Na^+ or the Ca^{2+} channel or via GABAergic transmission.[11] In addition to the major action site, the new AEDs tend to have several minor action sites. Pharmacological evaluations showed that LEV, PER, and LCM have unique binding sites and unique profiles (Table 1).[16]

In animal models of spontaneous- and induced epilepsy, LEV suppressed seizures,[17,18] but unlike other AEDs, it did not inhibit acute reactive seizures induced by maximal electroshock and the injection of pentylenetetrazol.[19] The LEV-induced inhibition of evoked abnormal firing was prolonged by more than 30 minutes in slice preparations after LEV was completely washed out from the perfusion.[20] While its action site was initially unknown, it was found to SV2A,[21] an isoform of integral membrane proteins, SV2A, and the most widespread isoform in all pre-synaptic terminals of the central nervous system (CNS).[22] In animal models, there appears to be a difference in the distribution of SV2A in the acute progressive and chronic states of epilepsy. In spontaneously epileptic rats with intractable epilepsy, there was a lower distribution of SV2A in the cerebrum and of synaptotagmin-1 in the epilepsy-related region.[23] We also had a result that immunohistochemical studies using isolated brain tissue from patients with intractable epilepsy yielded similar findings (Fig. 1). LEV decreased the vesicular release during high-frequency activity. The modulation of neuronal activity was a form of short-term depression that affected information transfer over a range of spike frequencies and stabilized cortical firing.[24] On the other hand, LEV delivered in an injectable solution suppressed the status epilepticus,[25] suggesting that LEV exerts its acute anticonvulsive effect via minor action sites in epileptic abnormal neurons like the L-type Ca^{2+} channel.[20,26]

PER is the first AED targeted on a receptor of glutamatergic transmission. AMPA receptors, primarily located on the post-synaptic membrane of excitatory synapses, are involved in fast excitatory signaling within and between brain regions. Their activation may lead to fast synaptic excitation.[27] Blockage of AMPA receptors globally across the brain has antiepileptic effects, and PER is an aryl-substituted 2-pyridone AMPA receptor antagonist whose side-effect profile in rodents and epileptic patients has been reported.[28]

LCM, a chiral functionalized amino acid, selectively enhances the slow inactivation of voltage-gated sodium channels and attenuates seizures.[29] Its profile in animal models of seizure and epilepsy is similar to that of AEDs like PHT and CBZ that block Na^+. Unlike these agents, LCM does not affect sustained repetitive firing on a time scale of hundreds of milliseconds nor does it affect fast inactivation of voltage-gated Na^+ channels.[29] LCM also binds to CRMP2.[30] CRMPs are a family of five intracellular phosphoproteins implicated in neurotrophic signaling and neuronal outgrowth. CRMP2 is most abundantly expressed in the adult brain. While there is no evidence that LCM directly binds to CRMP-2, it may be involved in an indirect functional interaction.[29]

Clinical Formulations in Use

I. Monotherapy

Table 2 presents the indication for the new AEDs. The effect of LTG and LEV on provoked seizures did not significantly differ from standard AEDs such as CBZ and VPA.[7–9] LTG and LEV are front raw-drug for monotherapy among new AEDs. In a comparison monotherapy study in which LEV was more rapidly titrated than the LTG arm, the efficacy and tolerability of LEV and LTG in patients with newly diagnosed focal and generalized epilepsy were not significantly

Table 1   Pharmacological site of action in popular old- and new generation

| Main action site	Drugs	Action site			
		Na⁺ channel	Ca²⁺ channel	GABAergic transmission	Others
Na⁺ channel					
	Phenytoin	◎		○	
	Carbamazepine	◎			
	Valproic acid	◎	○ T type	○	
	Zonisamide	○	○ T type		
	Topiramate	◎		○	○ AMPA-R
	Lamotrigine	◎	○ N, P type	○	
	Rufinamide	○			
	Oxcarbazepine	◎			
	Lacosamide	◎			○ CMRP2
GABAergic transmission					
	Phenobarbital			◎	
	Clonazepam			◎	
	Clobazam			◎	
	Vigabatrin			◎	
Ca²⁺ channel					
	Ethosuximide		◎ T type		
	Gabapentin		◎ α2δ subunit	○	
Others					
	Acetazolamide				◎ Inhibition of carbonic anhydrase activity
	Levetiracetam		○ T type		◎ SV2A ○ intracellular Ca²⁺ release
	Perampanel				◎ AMPA-R

bold letters: new antiepileptic drugs, ◎: major action site, ○: minor action site, AMPA-R: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, CMRP2: collapsin response mediator protein-2R, receptor.

different. However, adverse events, more prevalent with LEV than LTG, forced discontinuation of the study.[31)] Another study yielded similar results; the persistence rate of LTG was higher than of LEV.[32)] On the other hand, in a double-blind study in elderly patients with new-onset focal epilepsy, the effect on seizures and the drug retention rate of LEV and LTG did not differ significantly. Under identical administration protocols, LTG required slow titration; LEV was started at a lower dose and titrated slowly.[33)] These reports suggest that to improve the drug retention rate, new AEDs require slow titration especially at their first administration, though the patient dropout rate was similar to the other two studies in the early period of LEV administration.

II. Combination therapy

Add-on therapy is considered when one or two monotherapies fail to control seizures optimally. Treatment with AEDs should be optimized when the diagnosis of intractability is confirmed and surgery is not indicated in patients with epilepsy. For combination therapy, AEDs with other mechanisms of action are usually selected; the added AEDs must maximize efficacy and minimize the potential for adverse events. In patients receiving polytherapy,
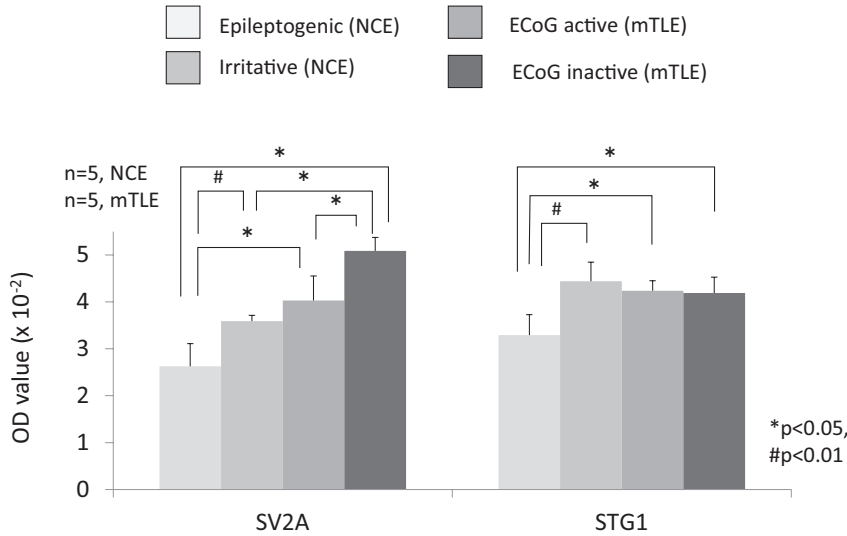
Fig. 1 Distribution of SV2A and synaptotagmin-1 in patients with intractable epilepsy. Based on chronic and intraoperative ECoG findings, samples were obtained from the epileptogenic- and the irritative area in patients with neocortical epilepsy, and from the EcoG-active and -inactive area in the temporal cortex of patients with mesial temporal lobe epilepsy. After immunohistochemical staining, the optical density of SV2A and synaptotagmin-1 was measured and its distribution was recorded. ECoG: electrocorticagraphy; mTLE: mesial temporal lobe epilepsy; NCE: neocortical epilepsy; OD: optical density; STG1: synaptotagmin-1.

Table 2 Indications for the new antiepileptic drugs

Drugs	Focal seizure	Generalized seizure				Epileptic spasms	Induced aggravation of seizure type/epilepsy syndrome
		Primary GTC	Absence	Myoclonic	Lennox-Gastaut		
Gabapentin	+						ABS, MCS, LGS
Topiramate	+	+	+	+	+	+	
Lamotrigine	+	+	+	(+)	+	+	MCS, JME, LGS, BECTS, Dravet syndrome
Levetiracetam	+	+	(+)	+	(+)	(+)	ABS
Rufinamide	+				+	+	Little information
Vigabatrin	+				(+)	+	ABS, MCS, LGS, Dravet syndrome
Oxcarbazepine	+						ABS, MCS, JME, LGS
Perampanel	+	+					Little information
Lacosamide	+						Little information

ABS: absence seizure, BECTS: benign epilepsy with centro-temporal spikes, GTC: generalized tonic-clonic, JME: juvenile myoclonic epilepsy, LGS: Lennox-Gastaut syndrome, MCS: myoclonic seizure, +: effective, (+): most likely effective.

drug interactions must be considered when enzyme-inducing AEDs such as PHT, CBZ, PB, and PRM or enzyme-inhibiting AEDs such as VPA are prescribed. The characteristics of new AEDs, i.e., the elicitation of fewer interactions and milder adverse effects, and their unique site of action render them useful for combination therapy.[11] LTG and TPM have an effect on liver enzymes, but no relevant interactions between other AEDs have been reported. Studies in animals have shown that AED combinations are more effective when drugs with different mechanisms of action are used. The most effective combination is a drug with a single- plus another with multiple mechanisms of action. In humans, combinations of a blocker of voltage-gated sodium channels plus a drug with multiple mechanisms of action may exert synergistic effects.[34] On the other hand, combinations of more than three drugs are not recommended because they rarely result in complete inhibition of epilepsy.[35] Further studies are needed to determine the efficacy and safety of AED combination therapy.

Indications for and Adverse Events with the New AEDs

The primary indication for the use of the new AEDs is partial seizures. While adverse effects have been documented, including seizure aggravation, they tend to be mild (Tables 2, 3). Skin rash has been reported in 2.8% of patients taking new AEDs, the incidence

Table 3 Adverse effects of new antiepileptic drugs

Adverse events	GBP	TPM	LTG	LEV	RFN	VGB	OXC	PER	LCM
CNS effects									
Somnolence	+	++	+	+	+	+		++	
Insomnia								+	
Sedation/psychomotor slowing		(+)							
Depression				(+)		+			
Behavioral problems		++		+	+	++			
Psychotic episodes	+	+		+		++		+	
Cognitive impairment		+					+		
Ataxia								+	+
Dizziness	+	++	+	+	+	+	++	++	++
Encephalopathy						++			
General issues									
Hypersensitivity		+	+				+		
Rash			+				+		
Fatigue		+			+			+	
Weight gain	+					+		+	
Weight loss		+			+				
Seizure aggravation	+				(+)	++		+	
Splanchnic and humoral system									
Leukopoenia							(+)		
Hyponatremia							+		
Gastrointestinal	(+)			(+)			+		
Pancreatitis	(+)								
Nephrolithiasis		(+)							

GBP: gabapentin, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PER: perampanel, RFM: rufinamide, TPM: topiramate, VGB: vigabatrin, ++: high risk, +: moderate risk, (+): minimal risk.

is 4.8% in patients treated with LTG and higher with the old AEDs (PHT, ZNS, and CBZ).[36)] TPM and LEV may induce fatigue and drowsiness.[10,11)] In the chronic phase, the incidence of adverse effects with the new AEDs is low,[15)] but TPM and PER, drugs that potentiate glutamatergic transmission, may elicit behavioral changes and cognition disorders. LEV also induces aggressiveness and cognition disorders.[37,38)] LEV and LTG present a lower teratogenic risk than the other AEDs,[14)] and the risk in patients treated with the combination of LTG and LEV is lower than when other combinations are used. Lower intelligence quotient (IQ) and autism have been reported in infants of women treated with high daily doses of VPA (> 1000 mg) during pregnancy.[39)] LTG and LEV feature a broad antiepileptic spectrum and their administration should be considered in women of child-bearing age.

Table 4 lists pharmacological interactions between new AEDs and combination drugs. GBP, LCM, VGB,

ZNS, and tiagabin are associated with the fewest- and LTG, OXC, RFM with the highest number of pharmacokinetic interactions.[12,13,40)]

AEDs must be titrated slowly to reduce the incidence of adverse effects. The titration of LTG is established and must be very slow to avoid severe skin rash. However, in elderly patients, titration compliance may be difficult. On the other hand, chewable and small tablet such as LTG are expected in higher drug compliance than solid and large ones such as LEV and VPA; this is an important consideration in the elderly with swallowing difficulties.

Clinical Implications in the Field of Neurosurgery

As there are few prospective double-blind studies indicating that new AEDs are better at inhibiting seizures, it is unlikely that they will soon replace traditional AEDs. Their primary advantage lies in

Table 4　Drug interaction of new antiepileptics with combination drugs

Drugs	Antiepileptics		Other drugs	
	Effects on other AEDs	Affected by other AEDs	Effects on other drugs	Affected by other drugs
Gabapentin				↓: aluminium hydroxide, magnesium hydroxide ↑: cimetidine, hydrocodone, morphine, naproxen
Topiramate	PER ↓↓ PB ↓ PHT ↑	↓↓: PHT, PB, PRM, CBZ ↓: VPA, OXC	oral contraceptive, imatinib, risperidone, glibenclamide, pioglitazone, risperidone, sumatriptan ↓ amitriptyline, diltiazem, haloperidol, lithium, metformin ↑	↑: amitriptyline, diltiazem, hydrochlothiazide, metformin, posaconazole, propranolol, sumatriptan
Lamotrigine	CZP, VPA, LEV ↓	↓↓: PHT, PB, PRM, CBZ ↓: CLB, RFM, OXC, PER ↑↑: VPA	aripiprazole, lithium, oral contraceptive (Pg component), quetiapine ↓ atorvastatin, olanzapine ↑	↓: acetaminophen, antituberculous agents, aripiprazole, atazanavir/ritonavir, fluoxetine, hormone replacement therapy, lithium, ropinavir/ritonavir, olanzapine, oral contraceptives, orlistat
Levetiracetam	OXC ↑	↓: PHT, PB, CBZ, LTG, OXC		↑: probenecid
Rufinamide	CBZ, LTG ↓ PHT, PB ↑	↓: PHT, PB, PRM, CBZ, VGB, OXC ↑: VPA	oral contraceptive ↓ triazolam ↑	
Vigabatrin	PHT, CBZ, RFM ↓ CBZ ↑			
Oxcarbazepine	PER ↓↓ CBZ, TPM, LTG, LEV, RFM ↓ PHT, PB ↑	↓: PHT, PB, CLB, LCM ↑: PER	oral contraceptive ↑ imatinib, felodipine ↓	↓: verapamil ↑: viloxazine
Perampanel		↓↓: PHT, CBZ, OXC	oral contraceptive ↓	↑: ketoconazole
Lacosamide	OXC ↓	↓: PHT, PB		

CBZ: carbamazepine, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PER: perampanel, Pg: progesterone, PHT: phenytoin, PRM: primidone, RCM: lacosamide, RFN: rufinamide, VGB: vigabatrin, VPA: valproic acid, ↓: minor decrease, ↓↓: clinically significant decrease, ↑: minor increase, ↑↑: clinically significant increase.

their retention and their side benefits that exceed those of traditional AEDs.

Although acute symptomatic seizures are primarily attributable to brain diseases, metabolic-, toxic-, and other systemic illnesses may also induce seizures.[41] The subcommittee of the American Academy of Neurology and the American Epilepsy Society presented recommendations on the treatment of adults with an unprovoked first seizure (Table 5).[42] Provoked seizures are acute symptomatic- and reactive seizures; the correspondence with this type or symptomatic focal seizures, including secondary generalization, is addressed below.

In 21–45% of adults, most recurrent seizures occur within 24 months after a first seizure. VPA is often chosen in the emergency state because its antiepileptic spectrum is wide and its adverse effects are less than other old AEDs. Selection of VPA may be acceptable in patients scheduled for surgery in the short term for its characteristics. However, antiepileptic potential of VPA is weak against focal seizures as shown in the recent reports that VPA monotherapy was an independent predictor of recurrent post-stroke seizures.[43] In such cases, the favorable characteristics of the new AEDs are advantageous (Table 6).

Table 5 Recommendation from the Subcommittee of the American Academy of Neurology and the American Epilepsy Society for treating unprovoked first seizures in adults

(1)	Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after the first seizure (21%–45%) (Level A).
(2)	Clinicians should also advise such patients that clinical factors associated with an increased risk for seizure recurrence include a prior brain insult such as a stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), or a nocturnal seizure (Level B).
(3)	Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk for a seizure recurrence in the 2 years subsequent to a first seizure (Level B), it may not improve QOL (Level C).
(4)	Clinicians should advise patients that over the longer term (> 3 years) immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B).
(5)	Patients should be advised that their risk for AED adverse events ranges from 7% to 31% (Level B) and that these adverse events are predominantly mild and reversible.

AED: antiepileptic drug; EEG: electroencephalogram; QOL: quality of life.

Table 6 Preferable indications for the administration of new antiepileptic drugs

Entity	Ponderable new AEDs
Background	
History of rush, allergy	LEV, GBP, TPM
Women of reproductive age	LEV, LTG*
Obesity	TPM, LTG, LEV, OXC
Elderly group	LEV, LTG, GBP
Comorbidity	
Depression	LTG, OXC
Cognitive impairment	LTG, GBP
Brain tumor	LEV, GBP
Migraine	TPM
Neuropathic pain	GBP, LTG, LCM
Hyperlipidemia	no-enzyme inducing AEDs
Co-medications	no-enzyme inducing AEDs

*: < 375 mg, AED: antiepileptic drug, GBP: gabapentin, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, TPM: topiramate.

The new AEDs may be beneficial for prophylactic and neuroprotective uses in patients with brain insults. This issue is addressed below.

Possibility of Neuroprotection in Neurocritical Care

The injury process after acute brain insults begins with energy failure creating excitotoxicity due to excessive glutamatergic activation. Oxidative stress is an important component of early injury together with excitotoxicity resulting from the excess formation of free radicals that target lipids, proteins, and DNAs. This damages cellular components and initiates a cascade ending in cell death. These deleterious biological events trigger inflammatory processes that are harmful.[44] Many AEDs, including new AEDs, have a neuroprotective potential because their antiepileptic mechanisms elicit antiexcitotoxicity.[45,46]

There are few clinical studies on the neuroprotective effect of AEDs. Trials in patients with acute ischemic and hemorrhagic stroke failed to support the use of GABA receptor agonists, chlormethiazole, or diazepam.[47] The neuroprotective effect of LTG as a sodium-channel blocker was examined in patients with secondary progressive multiple sclerosis, however, no significant effect was observed.[48]

Incidence of Seizures and Epilepsy due to Brain Insults

I. Stroke

Stroke is the leading cause of symptomatic epilepsy in adults. It accounts for up to one-third of newly diagnosed seizures among the elderly. The incidence of early seizures in acute stroke ranges from 3% to 33%, with 50–78% of the seizures occurring within the first 24 hours post-ictus; late seizures were observed in 2–4% of patients.[49] The occurrence of seizures within 24 hours of stroke is associated with a higher 30-day mortality rate. This may reflect severe neuronal damage,[50] and seizures during hospitalization predict a poor post-ischemic stroke prognosis.[51] About 3–5% of stroke patients will suffer a remote seizure and 55–66% of them will develop epilepsy.[49] In patients aged 18–50 years, the rate of post-stroke epilepsy and epilepsy with recurrent seizures was estimated to be 11.3% and

5.6%, respectively. The cumulative risk of epilepsy was 31%, 16%, and 5% in patients with intracranial hemorrhage, ischemic stroke, and transient ischemic attacks, respectively; the cumulative risk of epilepsy with recurrent seizures was 23%, 8%, and 4%, respectively, in these patients.[52] The risk for developing epilepsy was greatest in the first post-stroke year, however, it continued for at least a decade after the initial stroke.[53]

Intracerebral hemorrhage, subarachnoid hemorrhage, stroke of undetermined origin, and hyponatremia are risk factors for early seizures. Among ischemic strokes, the prevalent risk factors for early seizures were hyponatremia and hemorrhagic transformation. Risk factors for late seizures were a younger age and a cortical stroke site. In patients with intracerebral hemorrhage, the only risk factor for late seizures was the previous occurrence of early seizures. Risk factors of post-stroke epilepsy were the same as for late seizures.[54]

II. Traumatic brain injury

The average incidence of early seizures after traumatic brain injury (TBI) is reported to be 3.1%; it is 1.5% after mild-, 2.9% after moderate, and 17% after severe TBI.[55] Post-traumatic epilepsy (PTE) is reported in 10–20% of children with severe TBI.[56] Post-traumatic seizures are divided into immediate (< 24 hours), early (< 1 week), and late (> 1 week after injury) seizures. Both immediate and early seizures are designated as early post-traumatic seizures, and PTE is often defined as one or more unprovoked seizures occurring later than 1 week after TBI.[56] Early seizures are thought of as an epiphenomenon and a result of an acute injury; their occurrence does not always lead to the development of PTE. Mild head injury, head injury without skull fracture with either loss of consciousness or post-traumatic amnesia lasting less than 30 minutes does not increase the risk for epilepsy. The risk of PTE after moderate brain injury was 0.7% at 1 year and 1.6% at 5 years; after severe TBI it was 7.1% at 1 year and 11.5% at 5 years.[55] More than 90% of PTE episodes occurred within the first 10 years after trauma. The occurrence of PTE was significantly correlated with multiple risk factors, i.e., brain contusion with subdural hematoma, skull fracture, loss of consciousness or amnesia for more than 1 day, and an age of 65 years or older.[55]

III. Brain tumors

Between 30% and 50% of patients with brain tumors first present with seizures, and 30% or more will develop recurrent seizures.[57] Tumors involve a variety of epileptogenic factors including activation of glutaminergic NMDA receptors, immune-mediated neuronal damage, and anatomic changes in neuronal input pathways.[58] Because of the high risk of recurrence, AED treatment should be considered after the manifestation of a single seizure suspected to be due to the presence of a tumor.[57] Seizure control is an important pre-operative issue in patients with glioma.

Younger patients, tumors located in a temporal lobe, cortical involvement of the tumor, or containing oligodendroglial components increase the risk of seizures.[59] System Xc-, a cysteine/glutamate exchange complex is one of major glutamate transport protein on astrocyte membranes. Yuen et al. reported that increased expression of peritumoral system Xc- was an independent predictor of pre-operative seizure.[60] Schramm et al. proposed new subtype of grade II characterized by long-term epilepsy, longer survival, and lower recurrence rate have been described.[61] Immunohistochemical study of this subtype revealed a cellular proliferation below 1%, absence of nuclear p53 accumulation, and a lack of glial MAP2 and CD34 expression.[62] Gross total resection is the strongest predictors of seizure freedom in patients with low-grade gliomas.[59]

Prophylactic Use against Seizure and Epilepsy

Although AEDs are often administered prophylactically to inhibit reactive seizures after a brain insult, traditional AEDs do not prevent the development of epilepsy and there are no established guidelines for the prophylactic use of these drugs. The possible utility of new AEDs for prophylaxis has been explored in clinical studies.

I. Post-craniotomy

Post-craniotomy seizures are classified chronologically as immediate (within 24 hours), early (within 1 week), and late (all subsequent events).[63] Two-thirds of seizures occur in the first month after craniotomy, and the seizure risk persists for several months.[64] The incidence of seizures after supratentorial craniotomy for non-traumatic pathologies has been estimated to be between 15% and 20%.[65] There is little evidence that AEDs administered prophylactically are, or are not, effective for preventing post-craniotomy seizures. Most such studies compared LEV and PHT. In a head-to-head trial, prophylactic monotherapy with LEV in patients who had undergone supratentorial surgery elicited significantly fewer adverse events and resulted in a higher retention rate than PHT.[66,67] Another report showed that in patients treated with LEV, the incidence of seizures was significantly lower

(7.3%) than expected; it was 15–20% in patients who had not received AED prophylaxis.[66,68] In studies on the effect of the combination of intravenous plus the oral administration of AEDs, there was no significant difference attributable to the intravenous delivery of the drug. In fact, its discontinuation due to the elicitation of adverse side effects was rare in the studies using LEV and PHT.[69]

Although analgesia is not the primary role played by AEDs, the analgesic effect of GBP has been reported.[70] Its administration alleviated the acute post-operative pain of patients who had undergone craniotomy for supratentorial tumor resection and helped to reduce the need for pain medications.

II. Stroke

The routine use of AEDs does not prevent post-stroke epilepsy. Observational studies that evaluated the effect of the intravenous delivery of AEDs in the acute phase suggested that the chronic administration of PHT or fosphenytoin was associated with poor long-term neuropsychological outcomes in patients with SAH.[71] Similar problems were encountered when PHT was administered after intracerebral hemorrhage.[72] When LEV was used for seizure prophylaxis after SAH, its 3-day intravenous administration elicited a higher rate of in-hospital seizures than did an extended course of PHT; most of this increase was due to late seizures. This suggests that a longer prophylactic course is needed to minimize seizures post-SAH.[73] Despite similarities in the hemorrhage type and the severity of SAH at onset, patients treated with LEV manifested better cognition at the the time of discharge and fewer seizures thereafter than did patients treated with PHT.[74]

III. Traumatic brain injuries

The neuroprotective effect of the prophylactic administration of traditional AEDs and magnesium has been studied in large trials.[75,76] Neither VPA, CBZ, nor PHT prevented the development of epilepsy after moderate to severe TBI and they failed to reduce the rate of death and neurological disability. On the other hand, PHT and CBZ prevented the occurrence of early seizures in the first week after TBI. While magnesium exhibited a neuroprotective effect in a number of animal epilepsy models, it did not protect against PTE.

The prophylactic effect of LEV and PHT has been compared in patients with severe TBI. LEV is as effective as PHT for preventing early post-traumatic seizures.[77] While the long-term functional outcomes in TBI patients treated with PHT or LEV were not significantly different, the incidence of

fever during hospitalization was higher in patients receiving PHT.[78]

IV. Brain tumors

According to de Oliveira et al. 70% of their patients with primary brain tumors received prophylactic AEDs.[79] Its administration was discontinued in 14.1% of patients, mostly after a prolonged period and 27% of their patients on primary prophylaxis suffered seizures that tended to be associated with tumor progression. Yuan et al. performed a meta-analysis that included five observational studies and one RCT study.[80] Their investigation into the prophylactic efficacy of AEDs after glioma resection identified no significant difference between P450 enzyme-inducing- (PHT, CBZ, VPA) and non-enzyme-inducing AEDs (LEV) with respect to the prevention of late seizures. However, the tumors were of different histologies. Another evidence from a review concluded that AEDs should not be routinely administered because they failed to improve seizure control and because the incidence of adverse events was high.[81]

Use of the New AEDs considering Primary Diseases and Comorbidities

I. Management of stroke recurrence risk

While stroke is a causative factor of epilepsy in adults, two population-based cohort studies indicated that epilepsy increases the risk of stroke.[82,83] According to Wannamaker et al., after adjusting for covariables, the risk for a subsequent stroke in patients 35 years and older who suffered new-onset epilepsy was increased by 60% compared to the controls, and the median time to stroke was significantly shorter in epileptics than the controls (2.7 years vs. 3.2 years).[82] Comorbidity related to stroke was higher in their epilepsy group than in the controls. In a series reported by Chang et al., there were no prominent stroke-related comorbidities, however, among epileptics the incidence of both ischemic and hemorrhagic stroke was higher than in the general population.[83] In addition, younger patients with epilepsy and patients treated with high doses of AEDs had a high risk of stroke. Consequently, they concluded that the overall risk for both ischemic and hemorrhagic stroke increased as the AED exposure increased. Tan et al. reported that in epileptics, the thickness of the carotid intima-media appeared to be positively correlated with the duration of AED therapy.[84]

The enzyme-inducing AEDs, i.e., PHT, PB, CBZ, and PRM, increase the activity of the hepatic cytochrome P450 system involved in the synthesis of serum

cholesterol. Such AEDs increase total cholesterol as would be expected from the enzyme induction hypothesis[85]) and most studies indicated that their effects on specific lipid fractions favor an atherogenic profile. Other vascular risk markers, lipoprotein, CRP, and homocysteine, were increased by CBZ and PB, CBZ and PHT, and by CBZ, PHT, and PB, respectively.[86]) VPA is an enzyme-inhibiting drug; its administration results in a decreased production of cholesterol. However, it induces weight gain. A prospective study on children treated with VPA and followed for at least 2 years found that 40% developed obesity, and of those, 43% developed metabolic syndrome.[87]) Newer AEDs have minimal or no effect on hepatic enzymes.[88]) As patients taking TPM experienced a significant weight loss,[89]) its potential use in obese or overweight patients needs to be evaluated. The appropriateness of newer AEDs must be considered in patients with a higher risk of cerebro- and cardio-vascular disease.

II. Cognitive impairment and psychological comorbidities after stroke and TBI

Psychiatric comorbidities in epileptics have important clinical and therapeutic implications. The most frequent psychiatric diagnoses are psychoses, neuroses, mood disorders, personality disorders, and behavioral problems.[90]) In a population-based analysis, lifetime major depression was a significant issue after adjusting for covariates.[91])

Epilepsy is often accompanied by depression or a depressive state. Data from our outpatient clinic revealed a correlation between the depressive state and the quality of life (Fig. 2). Among
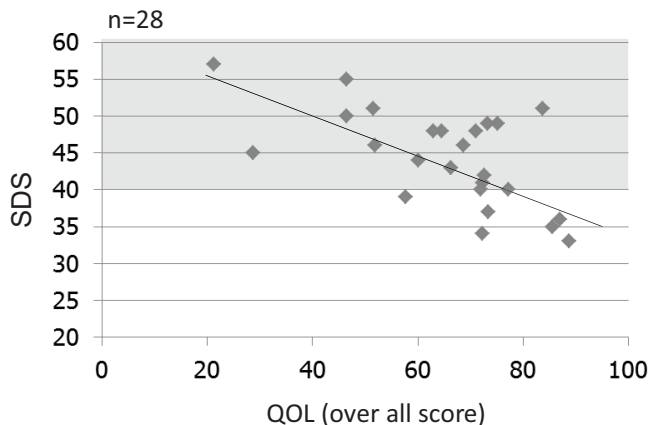
Fig. 2 Quality of life and depression in new epilepsy patients seen in the outpatient clinic. There was a correlation between the severity of depression and the overall QOLIE-31P-J score. An SDS score higher than 40 indicates a depressive tendency. QOL: quality of life; SDS: self-rating depression scale.

stroke patients, 36.2% suffered depression[92]) and based on the neuropsychological battery, the rate of patients with cognitive impairment without dementia increased to 26.8–39.5% 1 year after stroke onset.[93]) The incidence of post-stroke dementia is about 30%.[94]) TBI can elicit immediate and long-term seizures and epilepsy, mood changes, behavioral and personality problems, cognitive and motor deficits, movement disorders, and sleep problems.[95]) A recent meta-analysis indicates that TBI is associated with the development of neurological and psychiatric illnesses including depression, psychotic disorders, mild cognitive impairment, and dementia.[96])

AEDs have negative effects on cognitive function and they also induce depression. In adult epileptics newly started on an AED, CBZ, GBP, LTG, and VPA elicited fewer adverse cognitive effects[36]) and among first-generation AEDs, CBZ, PHT, ESM, and VPA had a lower risk for eliciting depression (< 1%) than other traditional AEDs.[97]) Among the newer AEDs used in adult epileptics, GBP and LTG had significantly fewer psychiatric/behavioral side effects while LEV elicited psychiatric side effects in fewer than 10% of patients. Multiple studies reported patients who discontinued LEV due to significant psychiatric symptoms including increased aggression, panic attacks, and behavior changes.[37,38]) VGB and OXC were associated with similarly low rates of psychiatric/behavioral side effects in several studies that included a small number of patients. Non-significant intermediate rates of psychiatric/behavioral side effects were attributed to TPM and ZNS.[98]) LTG has been demonstrated to effectively treat depressive symptoms independent of its anticonvulsant efficacy in patients with epilepsy[97]) and LTG may stimulate improvement in patients with impairment after severe brain injury.[99])

The patients' psychiatric history was the most significant non-drug related predictor of AED-related psychiatric/behavioral side effects.[98]) LTG, GBP, CBZ, and VPA may be a good choice in patients with cognitive impairment and expected higher psychiatric comorbidity.

III. Use of AEDs in elderly patients

As the incidence of epilepsy is much higher in older- than other population subgroups[100]) and as the rate of seizure recurrence is higher in the elderly, treatment with appropriate AEDs should be started after their first seizure. Multivariate logistic regression analysis indicated that among patients with cerebrovascular disease with/without dementia, with brain tumors, head injury, and other CNS conditions, the elderly were more likely to experience new-onset epilepsy.[101]) Stroke is the most common

cause of symptomatic epilepsy in older adults and 30–40% of all elderly epileptics had suffered a stroke.[5] Stroke-risk management and attention to psychiatric comorbidities are especially important in elderly patients. The most frequent diagnosis in a cohort of elderly patients with new-onset epilepsy was temporal lobe epilepsy with complex partial seizures without secondary generalization (47.1%). An etiological diagnosis was possible in nearly 50% of patients, including those with cerebrovascular disease. Non-lesional temporal lobe epilepsy was not uncommon. The response to antiepileptic medications, primarily at lower doses, was good (96.3%).[102] The serum albumin concentration is often reduced in the elderly.[103] AEDs with high protein binding rates, i.e., CBZ, PHT, VPA, and CLB have higher levels of free AEDs than expected by the serum concentration. The blood concentration of renally-excreted AEDs, i.e., GBP, TPM, and LEV, is increased due to reduced clearance.

LTG, GBP, and CBZ are recommended for patients with partial seizures and the drug retention rate is high in order the of LTG, GBP, and CBZ.[104] LEV is also effective and recommended in elderly patients with medical complications.[105]

IV. Patients requiring chemotherapy

In patients needing chemotherapy, a non-enzyme-inducing AED is preferred for their initial treatment to minimize the risk of drug interactions that adversely affect the outcome of anticancer chemotherapy. The risk of AED-induced adverse effects that inhibit the effectiveness of chemotherapy must be avoided. The risk of skin rash[106] is a motivation for selecting appropriate AEDs in patients receiving chemotherapy. LEV yielded good seizure reduction and efficaciously controlled seizures in both add-on and monotherapy.[58,107,108] Patients with a good treatment response manifested significantly stronger SV2A expression in tumor- and peritumor tissues than patients who did not show a good response.[109] The expression of SV2A around the tumor may predict the efficacy of LEV. Its most common toxicity manifested as somnolence (30%), psychosis (3%), and performance worsening.[58,107,108] In such patients and patients with psychiatric history, other drugs such as GBP, LTG, OXC, TPM, and ZNS should be considered.[110]

VPA exhibited both histone deacetylase inhibitor (HDACi) activity and anticancer effects.[111] In pre-clinical models it sensitized glioblastoma cells.[112] Chemo-radiation therapy with temozolomide and VPA resulted in a 2-month survival prolongation in glioblastoma patients[113] and a meta-analysis and a systematic review indicated that glioblastoma patients

treated with VPA may experience prolonged survival.[79] Bobustuc et al. report that LEV is the most potent O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein inhibitor, among several AEDs with diverse MGMT regulatory actions.[114] LEV enhances p53 binding on the MGMT promoter by recruiting the mSin3A/histone deacetylase 1 (HDAC1) corepressor complex. It inhibits the proliferation of malignant glioma cells and increases their sensitivity to the nonfunctional alkylating agent temozolomide.[114] In a multivariate analysis, the variables that were identified as significant prognostic factors for overall survival were the score on the pre-operative Karnofsky performance scale, MGMT promoter methylation, and the administration of LEV.[115] Thus, LEV may have a survival benefit in patients with glioblastoma undergoing temozolomide-based chemotherapy. Vecht and Wilms suggested initializing the anticonvulsant treatment with LEV and in the case of an inadequate response, the co-administration of VPA due to the possibility of synergistic effects.[116] Although VPA is a second-line AED to address focal seizures, Kerkhof et al. reported that seizure freedom was obtained in 77.8% of glioblastoma patients with ongoing seizures who were treated with VPA alone, in 69.5% who were on LEV alone, and in 60.3% undergoing VPA/LEV polytherapy.[112] In efforts to enhance the activity of LEV, it may be possible to replace VPA with TPM, LTG, and OXC.[116,117]

Conclusion

When treating patients with focal epilepsy due to brain insults, neurosurgeons must consider their age and gender and the residual disability resulting from the injury. In the critical phase, protection from seizures is the most important issue. In the chronic phase, attention must be paid to characteristic comorbidities and concurrent diseases in the selection of AEDs. While the view from cost-benefit relation may be required in using new AEDs at the moment, specific features of the new AEDs, i.e., fewer drug interactions, fewer chronic adverse events, and drug side benefits may render the new AEDs advantageous in epileptic patients with comorbidities and disabilities due to brain insults.

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were collected and analyzed under anonymization in linkable fashion.

Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest (COI) regarding this article according to the criteria of The Japan Neurosurgical Society. All authors completed the self-reported COI Disclosure Statement form via the website of the society.

References

1) Johannessen Landmark C, Patsalos PN: Drug interactions involving the new second- and third-generation antiepileptic drugs. *Expert Rev Neurother* 10: 119–140, 2010

2) Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, Mattson R, French JA, Perucca E, Tomson T; ILAE Subcommission on AED Guidelines: Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 54: 551–563, 2013

3) Nunes VD, Sawyer L, Neilson J, Sarri G, Cross JH: Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. *BMJ* 344: e281, 2012

4) Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S: ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 55: 475–482, 2014

5) Brodie MJ, Elder AT, Kwan P: Epilepsy in later life. *Lancet Neurol* 8: 1019–1030, 2009

6) Zaccara G, Giovannelli F, Cincotta M, Loiacono G, Verrotti A: Adverse events of placebo-treated, drug-resistant, focal epileptic patients in randomized controlled trials: a systematic review. *J Neurol* 262: 501–515, 2015

7) Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group: The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 369: 1000–1015, 2007

8) Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD

Study group: The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 369: 1016–1026, 2007

9) Trinka E, Marson AG, Van Paesschen W, Kälviäinen R, Marovac J, Duncan B, Buyle S, Hallström Y, Hon P, Muscas GC, Newton M, Meencke HJ, Smith PE, Pohlmann-Eden B; KOMET Study Group: KOMET: an unblinded, randomised, two parallel-group, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy. *J Neurol Neurosurg Psychiatr* 84: 1138–1147, 2013

10) French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE, Sachdeo RC, Beydoun A, Glauser TA; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society: Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 62: 1252–1260, 2004

11) French JA, Faught E: Rational polytherapy. *Epilepsia* 50(Suppl 8): 63–68, 2009

12) Patsalos PN: Drug interactions with the newer antiepileptic drugs (AEDs)—part 1: pharmacokinetic and pharmacodynamic interactions between AEDs. *Clin Pharmacokinet* 52: 927–966, 2013

13) Patsalos PN: Drug interactions with the newer antiepileptic drugs (AEDs)—part 2: pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. *Clin Pharmacokinet* 52: 1045–1061, 2013

14) Reimers A: New antiepileptic drugs and women. *Seizure* 23: 585–591, 2014

15) Elger CE, Schmidt D: Modern management of epilepsy: a practical approach *Epilepsy Behav* 12: 501–539, 2008

16) Stephen LJ, Brodie MJ: Pharmacotherapy of epilepsy: newly approved and developmental agents. *CNS Drugs* 25: 89–107, 2011

17) Bouwman BM, van Rijn CM: Effects of levetiracetam on spike and wave discharges in WAG/Rij rats. *Seizure* 13: 591–594, 2004

18) Ji-qun C, Ishihara K, Nagayama T, Serikawa T, Sasa M: Long-lasting antiepileptic effects of levetiracetam against epileptic seizures in the spontaneously epileptic rat (SER): differentiation of levetiracetam from conventional antiepileptic drugs. *Epilepsia* 46: 1362–1370, 2005

19) Klitgaard H: Levetiracetam: the preclinical profile of a new class of antiepileptic drugs? *Epilepsia* 42(Suppl 4): 13–18, 2012

20) Hanaya R, Kiura Y, Serikawa T, Kurisu K, Arita K, Sasa M: Modulation of abnormal synaptic transmission in hippocampal CA3 neurons of spontaneously epileptic rats (SERs) by levetiracetam. *Brain Res Bull* 86: 334–339, 2011

21) Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B: The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci USA* 101: 9861–9866, 2004

22) Mendoza-Torreblanca JG, Vanoye-Carlo A, Phillips-Farfán BV, Carmona-Aparicio L, Gómez-Lira G: Synaptic vesicle protein 2A: basic facts and role in synaptic function. *Eur J Neurosci* 38: 3529–3539, 2013

23) Hanaya R, Hosoyama H, Sugata S, Tokudome M, Hirano H, Tokimura H, Kurisu K, Serikawa T, Sasa M, Arita K: Low distribution of synaptic vesicle protein 2A and synaptotagimin-1 in the cerebral cortex and hippocampus of spontaneously epileptic rats exhibiting both tonic convulsion and absence seizure. *Neuroscience* 221: 12–20, 2012

24) Yang X, Bognar J Jr, He T, Mohammed M, Niespodziany I, Wolff C, Esguerra M, Rothman SM, Dubinsky JM: Brivaracetam augments short-term depression and slows vesicle recycling. *Epilepsia* 56: 1899–1909, 2015

25) Atmaca MM, Orhan EK, Bebek N, Gurses C: Intravenous levetiracetam treatment in status epilepticus: a prospective study. *Epilepsy Res* 114: 13–22, 2015

26) Yan HD, Ishihara K, Seki T, Hanaya R, Kurisu K, Arita K, Serikawa T, Sasa M: Inhibitory effects of levetiracetam on the high-voltage-activated L-type Ca^{2+} channels in hippocampal CA3 neurons of spontaneously epileptic rat (SER). *Brain Res Bull* 90: 142–148, 2013

27) Rogawski MA: AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand, Suppl* 9–18, 2013

28) Zwart R, Sher E, Ping X, Jin X, Sims JR Jr, Chappell AS, Gleason SD, Hahn PJ, Gardinier K, Gernert DL, Hobbs J, Smith JL, Valli SN, Witkin JM: Perampanel, an antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, for the treatment of epilepsy: studies in human epileptic brain and nonepileptic brain and in rodent models. *J Pharmacol Exp Ther* 351: 124–133, 2014

29) Rogawski MA, Tofighy A, White HS, Matagne A, Wolff C: Current understanding of the mechanism of action of the antiepileptic drug lacosamide. *Epilepsy Res* 110: 189–205, 2015

30) Wilson SM, Khanna R: Specific binding of lacosamide to collapsin response mediator protein 2 (CRMP2) and direct impairment of its canonical function: implications for the therapeutic potential of lacosamide. *Mol Neurobiol* 51: 599–609, 2015

31) Rosenow F, Schade-Brittinger C, Burchardi N, Bauer S, Klein KM, Weber Y, Lerche H, Evers S, Kovac S, Hallmeyer-Elgner S, Winkler G, Springub J, Niedhammer M, Roth E, Eisensehr I, Berrouschot J, Arnold S, Schröder M, Beige A, Oertel WH, Strzelczyk A, Haag A, Reif PS, Hamer HM; LaLiMo Study Group: The LaLiMo Trial: lamotrigine compared with levetiracetam in the initial 26 weeks of monotherapy for focal and generalised epilepsy—an open-label, prospective, randomised controlled multicenter study. *J Neurol Neurosurg Psychiatr* 83: 1093–1098, 2012

32) Bootsma HP, Ricker L, Hekster YA, Hulsman J, Lambrechts D, Majoie M, Schellekens A, de Krom M, Aldenkamp AP: The impact of side effects on long-term retention in three new antiepileptic drugs. *Seizure* 18: 327–331, 2009

33) Werhahn KJ, Trinka E, Dobesberger J, Unterberger I, Baum P, Deckert-Schmitz M, Kniess T, Schmitz B, Bernedo V, Ruckes C, Ehrlich A, Krämer G: A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* 56: 450–459, 2015

34) Giussani G, Beghi E: Does mechanism of drug action matter to inform rational polytherapy in epilepsy? *CNS Neurol Disord Drug Targets* 12: 426–435, 2013

35) Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P: Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 78: 1548–1554, 2012

36) Arif H, Buchsbaum R, Weintraub D, Pierro J, Resor SR Jr, Hirsch LJ: Patient-reported cognitive side effects of antiepileptic drugs: predictors and comparison of all commonly used antiepileptic drugs. *Epilepsy Behav* 14: 202–209, 2009

37) Bernett A, Phenis R, Fonkem E, Aceves J, Kirmani B, Cruz-Laureano D: Neurobehavioral effects of levetiracetam in brain tumor related epilepsy. *Front Neurol* 4: 99, 2013

38) Wieshmann UC, Baker GA: Self-reported feelings of anger and aggression towards others in patients on levetiracetam: data from the UK antiepileptic drug register. *BMJ Open* 3. pii: e002564, 2013

39) Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group: Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 12: 244–252, 2013

40) Zaccara G, Perucca E: Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 16: 409–431, 2014

41) Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA: Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 51: 671–675, 2010

42) Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, Liferidge AT, Martello JP, Kanner AM, Shinnar S, Hopp JL, French JA: Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 84: 1705–1713, 2015

43) Tanaka T, Yamagami H, Ihara M, Motoyama R, Fukuma K, Miyagi T, Nishimura K, Toyoda K, Nagatsuka K: Seizure outcomes and predictors of recurrent

post-stroke seizure: a retrospective observational cohort study. *PLoS ONE* 10: e0136200, 2015

44) Juul SE, Ferriero DM: Pharmacologic neuroprotective strategies in neonatal brain injury. *Clin Perinatol* 41: 119–131, 2014

45) Pitkänen A: Drug-mediated neuroprotection and antiepileptogenesis: animal data. *Neurology* 59(9 Suppl 5): 27–33, 2002

46) Stepień K, Tomaszewski M, Czuczwar SJ: Profile of anticonvulsant activity and neuroprotective effects of novel and potential antiepileptic drugs—an update. *Pharmacol Rep* 57: 719–733, 2005

47) Liu J, Wang LN: Gamma aminobutyric acid (GABA) receptor agonists for acute stroke. *Cochrane Database Syst Rev* 8: CD009622, 2014

48) Kapoor R, Furby J, Hayton T, Smith KJ, Altmann DR, Brenner R, Chataway J, Hughes RA, Miller DH: Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Neurol* 9: 681–688, 2010

49) Ryvlin P, Montavont A, Nighoghossian N: Optimizing therapy of seizures in stroke patients. *Neurology* 67 (Suppl 4): S3–S9, 2006

50) Chung JM: Seizures in the acute stroke setting. *Neurol Res* 36: 403–406, 2014

51) Huang CW, Saposnik G, Fang J, Steven DA, Burneo JG: Influence of seizures on stroke outcomes: a large multicenter study. *Neurology* 82: 768–776, 2014

52) Arntz R, Rutten-Jacobs L, Maaijwee N, Schoonderwaldt H, Dorresteijn L, van Dijk E, de Leeuw FE: Post-stroke epilepsy in young adults: a long-term follow-up study. *PLoS ONE* 8: e55498, 2013

53) Adelöw C, Andersson T, Ahlbom A, Tomson T: Prior hospitalization for stroke, diabetes, myocardial infarction, and subsequent risk of unprovoked seizures. *Epilepsia* 52: 301–307, 2011

54) Serafini A, Gigli GL, Gregoraci G, Janes F, Cancelli I, Novello S, Valente M: Are early seizures predictive of epilepsy after a stroke? Results of a population-based study. *Neuroepidemiology* 45: 50–58, 2015

55) Annegers JF, Hauser WA, Coan SP, Rocca WA: A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 338: 20–24, 1998

56) Pearl PL, McCarter R, McGavin CL, Yu Y, Sandoval F, Trzcinski S, Atabaki SM, Tsuchida T, van den Anker J, He J, Klein P: Results of phase II levetiracetam trial following acute head injury in children at risk for posttraumatic epilepsy. *Epilepsia* 54: e135–e137, 2013

57) Perucca E: Optimizing antiepileptic drug treatment in tumoral epilepsy. *Epilepsia* 54(Suppl 9): 97–104, 2013

58) Newton HB, Goldlust SA, Pearl D: Retrospective analysis of the efficacy and tolerability of levetiracetam in brain tumor patients. *J Neurooncol* 78: 99–102, 2006

59) Rudà R, Bello L, Duffau H, Soffietti R: Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. *Neuro Oncol* 14(Suppl 4): iv55–iv64, 2012

60) Yuen TI, Morokoff AP, Bjorksten A, D'Abaco G, Paradiso L, Finch S, Wong D, Reid CA, Powell KL, Drummond KJ, Rosenthal MA, Kaye AH, O'Brien TJ: Glutamate is associated with a higher risk of seizures in patients with gliomas. *Neurology* 79: 883–889, 2012

61) Schramm J, Luyken C, Urbach H, Fimmers R, Blümcke I: Evidence for a clinically distinct new subtype of grade II astrocytomas in patients with long-term epilepsy. *Neurosurgery* 55: 340–347; discussion 347–348, 2004

62) Blümcke I, Luyken C, Urbach H, Schramm J, Wiestler OD: An isomorphic subtype of long-term epilepsy-associated astrocytomas associated with benign prognosis. *Acta Neuropathol* 107: 381–388, 2004

63) Foy PM, Copeland GP, Shaw MD: The natural history of postoperative seizures. *Acta Neurochir (Wien)* 57: 15–22, 1981

64) North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB: Phenytoin and postoperative epilepsy. A double-blind study. *J Neurosurg* 58: 672–677, 1983

65) Weston J, Greenhalgh J, Marson AG: Antiepileptic drugs as prophylaxis for post-craniotomy seizures. *Cochrane Database Syst Rev* 3: CD007286, 2015

66) Kern K, Schebesch KM, Schlaier J, Hansen E, Feigl GC, Brawanski AT, Lange M: Levetiracetam compared to phenytoin for the prevention of postoperative seizures after craniotomy for intracranial tumours in patients without epilepsy. *J Clin Neurosci* 19: 99–100, 2012

67) Milligan TA, Hurwitz S, Bromfield EB: Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. *Neurology* 71: 665–669, 2008

68) Gokhale S, Khan SA, Agrawal A, Friedman AH, McDonagh DL: Levetiracetam seizure prophylaxis in craniotomy patients at high risk for postoperative seizures. *Asian J Neurosurg* 8: 169–173, 2013

69) Fuller KL, Wang YY, Cook MJ, Murphy MA, D'Souza WJ: Tolerability, safety, and side effects of levetiracetam versus phenytoin in intravenous and total prophylactic regimen among craniotomy patients: a prospective randomized study. *Epilepsia* 54: 45–57, 2013

70) Türe H, Sayin M, Karlikaya G, Bingol CA, Aykac B, Türe U: The analgesic effect of gabapentin as a prophylactic anticonvulsant drug on postcraniotomy pain: a prospective randomized study. *Anesth Analg* 109: 1625–1631, 2009

71) Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, Connolly ES, Mayer SA, Fitzsimmons BF: Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke* 36: 583–587, 2005

72) Naidech AM, Garg RK, Liebling S, Levasseur K, Macken MP, Schuele SU, Batjer HH: Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke* 40: 3810–3815, 2009

73) Murphy-Human T, Welch E, Zipfel G, Diringer MN, Dhar R: Comparison of short-duration levetiracetam with extended-course phenytoin for seizure

prophylaxis after subarachnoid hemorrhage. *World Neurosurg* 75: 269–274, 2011

74) Taylor S, Heinrichs RJ, Janzen JM, Ehtisham A: Levetiracetam is associated with improved cognitive outcome for patients with intracranial hemorrhage. *Neurocrit Care* 15: 80–84, 2011

75) Glötzner FL, Haubitz I, Miltner F, Kapp G, Pflughaupt KW: [Seizure prevention using carbamazepine following severe brain injuries]. *Neurochirurgia (Stuttg)* 26: 66–79, 1983

76) Temkin NR: Preventing and treating posttraumatic seizures: the human experience. *Epilepsia* 50(Suppl 2): 10–13, 2009

77) Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT, Stippler M, Fischer M, Sauber-Schatz EK, Fabio A, Darby JM, Okonkwo DO: Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus* 25: E3, 2008

78) Gabriel WM, Rowe AS: Long-term comparison of GOS-E scores in patients treated with phenytoin or levetiracetam for posttraumatic seizure prophylaxis after traumatic brain injury. *Ann Pharmacother* 48: 1440–1444, 2014

79) de Oliveira JA, Santana IA, Caires IQ, Caires-Lima R, Miranda VC, Protásio BM, Rocha LS, Braga HF, Mencarini AM, Teixeira MJ, Castro LH, Feher O: Antiepileptic drug prophylaxis in primary brain tumor patients: is current practice in agreement to the consensus? *J Neurooncol* 120: 399–403, 2014

80) Yuan Y, Xiang W, Qing M, Yanhui L, Jiewen L, Yunhe M: Survival analysis for valproic acid use in adult glioblastoma multiforme: a meta-analysis of individual patient data and a systematic review. *Seizure* 23: 830–835, 2014

81) Sayegh ET, Fakurnejad S, Oh T, Bloch O, Parsa AT: Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence. *J Neurosurg* 121: 1139–1147, 2014

82) Wannamaker BB, Wilson DA, Malek AM, Selassie AW: Stroke after adult-onset epilepsy: a population-based retrospective cohort study. *Epilepsy Behav* 43: 93–99, 2015

83) Chang CS, Liao CH, Lin CC, Lane HY, Sung FC, Kao CH: Patients with epilepsy are at an increased risk of subsequent stroke: a population-based cohort study. *Seizure* 23: 377–381, 2014

84) Tan TY, Lu CH, Chuang HY, Lin TK, Liou CW, Chang WN, Chuang YC: Long-term antiepileptic drug therapy contributes to the acceleration of atherosclerosis. *Epilepsia* 50: 1579–1586, 2009

85) Gibbons GF, Mitropoulos KA: The rôle of cytochrome P-450 in cholesterol biosynthesis. *Eur J Biochem* 40: 267–273, 1973

86) Lopinto-Khoury C, Mintzer S: Antiepileptic drugs and markers of vascular risk. *Curr Treat Options Neurol* 12: 300–308, 2010

87) Verrotti A, Manco R, Agostinelli S, Coppola G, Chiarelli F: The metabolic syndrome in overweight epileptic patients treated with valproic acid. *Epilepsia* 51: 268–273, 2010

88) Benedetti MS: Enzyme induction and inhibition by new antiepileptic drugs: a review of human studies. *Fundam Clin Pharmacol* 14: 301–319, 2000

89) Pickrell WO, Lacey AS, Thomas RH, Smith PE, Rees MI: Weight change associated with antiepileptic drugs. *J Neurol Neurosurg Psychiatr* 84: 796–799, 2013

90) Gaitatzis A, Trimble MR, Sander JW: The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 110: 207–220, 2004

91) Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S: Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 48: 2336–2344, 2007

92) Bour A, Rasquin S, Aben I, Boreas A, Limburg M, Verhey F: A one-year follow-up study into the course of depression after stroke. *J Nutr Health Aging* 14: 488–493, 2010

93) Serrano S, Domingo J, Rodríguez-Garcia E, Castro MD, del Ser T: Frequency of cognitive impairment without dementia in patients with stroke: a two-year follow-up study. *Stroke* 38: 105–110, 2007

94) Leys D, Hénon H, Mackowiak-Cordoliani MA, Pasquier F: Poststroke dementia. *Lancet Neurol* 4: 752–759, 2005

95) Szaflarski JP, Nazzal Y, Dreer LE: Post-traumatic epilepsy: current and emerging treatment options. *Neuropsychiatr Dis Treat* 10: 1469–1477, 2014

96) Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, Miller BL, Guskiewicz KM, Berger MS, Kramer JH, Welsh-Bohmer KA: Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg* Aug 28: 1–16, 2015 [Epub ahead of print]

97) Miller JM, Kustra RP, Vuong A, Hammer AE, Messenheimer JA: Depressive symptoms in epilepsy: prevalence, impact, aetiology, biological correlates and effect of treatment with antiepileptic drugs. *Drugs* 68: 1493–1509, 2008

98) Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ: Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. *Epilepsy Behav* 10: 105–110, 2007

99) Showalter PE, Kimmel DN: Stimulating consciousness and cognition following severe brain injury: a new potential clinical use for lamotrigine. *Brain Inj* 14: 997–1001, 2000

100) Kirmani BF, Robinson DM, Kikam A, Fonkem E, Cruz D: Selection of antiepileptic drugs in older people. *Curr Treat Options Neurol* 16: 295, 2014

101) Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC: New-onset epilepsy risk factors in older veterans. *J Am Geriatr Soc* 57: 237–242, 2009

102) Tanaka A, Akamatsu N, Shouzaki T, Toyota T, Yamano M, Nakagawa M, Tsuji S: Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. *Seizure* 22: 772–775, 2013

103) Greenblatt DJ: Reduced serum albumin concentration in the elderly: a report from the Boston

Collaborative Drug Surveillance Program. *J Am Geriatr Soc* 27: 20–22, 1979

104) Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, Spitz M, Frederick T, Towne A, Carter GS, Marks W, Felicetta J, Tomyanovich ML; VA Cooperative Study 428 Group: New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 64: 1868–1873, 2005

105) Brodie MJ, Overstall PW, Giorgi L: Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res* 37: 81–87, 1999

106) Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, Resor SR, Hirsch LJ: Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 68: 1701–1709, 2007

107) Usery JB, Michael LM 2nd, Sills AK, Finch CK: A prospective evaluation and literature review of levetiracetam use in patients with brain tumors and seizures. *J Neurooncol* 99: 251–260, 2010

108) Zachenhofer I, Donat M, Oberndorfer S, Roessler K: Perioperative levetiracetam for prevention of seizures in supratentorial brain tumor surgery. *J Neurooncol* 101: 101–106, 2011

109) de Groot M, Aronica E, Heimans JJ, Reijneveld JC: Synaptic vesicle protein 2A predicts response to levetiracetam in patients with glioma. *Neurology* 77: 532–539, 2011

110) Maschio M, Dinapoli L: Lecture: profile of risks and benefits of new antiepileptic drugs in brain tumor-related epilepsy. *Neurol Sci* 32(Suppl 2): S259–S262, 2011

111) Masoudi A, Elopre M, Amini E, Nagel ME, Ater JL, Gopalakrishnan V, Wolff JE: Influence of valproic acid on outcome of high-grade gliomas in children. *Anticancer Res* 28: 2437–2442, 2008

112) Krauze AV, Myrehaug SD, Chang MG, Holdford DJ, Smith S, Shih J, Tofilon PJ, Fine HA, Camphausen K: A phase 2 study of concurrent radiation therapy, temozolomide, and the histone deacetylase inhibitor valproic acid for patients with glioblastoma. *Int J Radiat Oncol Biol Phys* 92: 986–992, 2015

113) Kerkhof M, Dielemans JC, van Breemen MS, Zwinkels H, Walchenbach R, Taphoorn MJ, Vecht CJ: Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. *Neuro-oncology* 15: 961–967, 2013

114) Bobustuc GC, Baker CH, Limaye A, Jenkins WD, Pearl G, Avgeropoulos NG, Konduri SD: Levetiracetam enhances p53-mediated MGMT inhibition and sensitizes glioblastoma cells to temozolomide. *Neuro-oncology* 12: 917–927, 2010

115) Kim YH, Kim T, Joo JD, Han JH, Kim YJ, Kim IA, Yun CH, Kim CY: Survival benefit of levetiracetam in patients treated with concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide for glioblastoma multiforme. *Cancer* 121: 2926–2932, 2015

116) Vecht CJ, Wilms EB: Seizures in low- and high-grade gliomas: current management and future outlook. *Expert Rev Anticancer Ther* 10: 663–669, 2010

117) Kargiotis O, Markoula S, Kyritsis AP: Epilepsy in the cancer patient. *Cancer Chemother Pharmacol* 67: 489–501, 2011