A Review on Recent Treatment on Epilepsy

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Abstract- *This paper reviews advances in epilepsy in recent years with a stress on therapeutics and underlying mechanisms, including epilepsy drug and surgical treatments. This article reviews the treatment approaches. It is an uncommon but important clinical problem with high mortality and morbidity rates. There are not any controlled or randomized studies, and then therapy has got to be supported clinical reports and opinion. Complete seizure control is achieved in 40–50% of all epileptic patients with drug treatment, as reported in most epidemiological studies. Many effective antiepileptic drugs with a favorable profile are available in Switzerland, allowing treatment tailored to the patient's needs. Epilepsy surgery may be a viable option for these patients. It requires in-depth evaluation in specialized centers, and is related to complete seizure control in 50–90% of the patients, depending on the lesion type and site. Only for patients in whom surgery cannot be offered should neuromodulation treatments be considered. In the present review, we outline a practical approach for the various steps in therapeutic decisions and that we summaries the profiles of recent antiepileptic drugs also outcome of surgical and neuromodulatory therapies. The goal of any approach should be to get complete seizure control. In general, if two antiepileptic drugs are not successful, in-depth evaluation of the patient in a specialized center is strongly recommended.*

Keywords- Epilepsy • Classification, status epilepticus, antiepileptic drugs.

I. INTRODUCTION

The prevalence of epilepsy is 0.5–1%, with an overall rate of complete seizure control in 40–50% of epileptic patients. "Epilepsy" has got to be differentiated from acute symptomatic seizures (table 1) and diseases that mimic epileptic seizures (table 2). Acute symptomatic seizures, previously also called "provoked seizures", don't meet the standards of this definition, and thus don't represent "epilepsy". Table 1 gives an summary of the foremost frequent acute insults. In the majority of cases, they are doing not need antiepileptic treat- ment (exceptions include recurrent alcohol withdrawal or other recurrent acute toxicometabolic conditions that can- not be controlled). Definitions in epilepsy have always been problematic. The disorder is characterised by seizures but not all seizures are thanks to epilepsy—febrile seizures or drug induced seizures, for instance. Earlier classifications sought to reconcile these difficulties by describing different electroclinical syndromes but new data from modern imaging and genetics need to be incorporated. This is the case, for instance , during a patient whose first seizure led to the invention of a tumour on resonance imaging (MRI), or an 18-year-old with generalised polyspike- wave discharges under hyperventilation on a typical electroencephalogram (EEG), indicating the presence of juvenile myoclonic epilepsy. The new definition of epilepsy changes the interpretation of older epidemiology studies, which still used the definition of two spontaneous seizures within >24 h, but matches clinical experience in most cases.

Tonic–clonic status epileptics is a medical emergency. Treatment is aimed at stopping seizures largely in order to avoid cerebral damage and other morbidity. Diagnosis is difficult because in practice, the diagnostic electrical hallmark of epilepsy could also be absent interictally, especially in adults or if seizures are infrequent and interictal epileptiform discharges may occasionally be present in those without seizures. Moreover, in some instances, an ''epileptic EEG'' could also be related to an epileptic encephalopathy, during which overt seizures could also be few or none, like Landau–Kleffner syndrome, and a cognitive disorder dominates the presentation. The International League Against Epilepsy recently consulted in an effort to synthesise a consensus view, whose output are going to be published in 2017. The result promises to be useful and pragmatic, recognizing that the syndromes are multifaceted; anybody case defined by an association of clinical, electrophysiological, etiological and comorbid factors. It also accepts that it's not always known if seizures are a part of focal or grand mal epilepsy which in some cases, like tuberous sclerosis, genetic and structural causes overlap. Some terms are going to be dropped, for instance , childhood epilepsies where the seizures remit are going to be called pharmacoresponsive instead of benign, recognizing that children whose seizures remit may nevertheless have significant persisting psychosocial comorbidities. This is the case, for example, in a patient whose first seizure led to the discovery of a tumour on magnetic resonance ima- ging (MRI), or an 18-year-old with generalised polyspike- wave

discharges under hyperventilation on a standard elec- troencephalogram (EEG), indicating the presence of juvenile myoclonic epilepsy. The ILAE has also pondered the question of whether one seizure could also be considered to be epilepsy and concluded that it's going to if there's a greater than 60% chance of another seizure; a risk conferred by the presence of EEG spikes or a serious structural aetiology. Epilepsy may be considered to have gone away after ten years with no sei- zures and with no treatment. Some frontal lobe epilepsies may be particularly diffi- cult to diagnose, often with non- diagnostic ictal scalp EEGs and some were initially considered to be a movement disorder, e.g. ‘‘paroxysmal nocturnal dystonia’’ in which its epileptic basis was shown later. The sit- uation has become more complex with the invention that patients with lobe epilepsy can also have epileptic nocturnal wandering, with similarities to parasomnias and also brief nocturnal movements which are not due to sei- zure discharges but may be a release phenomenon of interictal discharges. They may suffer also from non- epileptic parasomnias more frequently than the overall population. In the new classification, the phenomenon are going to be renamed ‘‘Sleep-related hypermotor epilepsy (SHE)’’. Especially, the important question of when to introduce an antiepileptic treatment remains subject of ongoing discus- sion. In 2015, the American Association of Neurology is- sued new recommendations, giving level A evidence for an increased chance of a recurrent seizure for adult pa- tients, greatest within the first 2 years after a primary seizure (21–45%). However, evidence in favour of risk reduction when directly starting anticonvulsant (AED) therapy, as compared with a delay of treatment pending a second seizure, is merely level B, compared with level B evidence. The aim of any epilepsy therapy should be the sup- pression of all seizures. Drug studies showed that 40–50% of patients with focal epilepsy, and about 15% of patients with idopathic generalised epilepsy (in the new termin- ology now called “genetic generalised epilepsy”) are re- fractory to medical treatment. Pharmacoresistant epilepsy (PRE) is diagnosed if two or more AEDs don't cause complete seizure control, despite regular drug intake of sufficiently high dosages as determined by regular meas- urement of serum levels (preferentially in the morning or before next drug intake). The chance to regulate seizures with a 3rd drug is merely 2%. There are several reasons why drugs don't work (table 4). Therefore, PRE requires prompt evaluation to determine possible reasons, usually as an inpatient evaluation for a 7–31% incidence of adverse effects from AED ther- apy, but which are mild and reversible. There is only weak evidence that immediate AED therapy, as compared with awaiting a second seizure, might not improve quality of life (level C). It has been claimed that a number of this evidence is predicated on a really few old studies. In the case of pri- or brain insult such as stroke or trauma, as well as in the presence of epileptiform abnormalities on the EEG, evid- ence is level A for the increased risk for seizure recurrence. However, for the association of clinical factors such as brain-imaging abnormality or a nocturnal seizure, eviden- ce is only level B. The guideline’s summary conclusion is therefore that “… recommendations whether to initiate im- mediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recur- rence against the AEs [adverse events] of AED therapy, consider educated patient preferences, and advise that im- mediate treatment will not improve the long-term prognos- is for seizure remission but will reduce seizure risk over the subsequent 2 years.” This emphasises that guidelines summarise current evidence, but cannot replace individual judgment in the case of every specific patient.

Table 1: Possible causes of acute symptomatic seizures.

Insult	**Clinical features**
Illicit drugs	Amphetamine-like drugs, cocaine, crack, angel dust (phencyclidine) Less likely for heroin or cannabis
Infections	Within <7–14 d Viral encephalitis Bacterial meningitis Degenerative phase of neurocysticercosis
Medication	Chlorpromazine, clozapine, Maprotiline, clomipramine, Bupropion, meperidine, Flumazenil, cyclic antidepressants, Theophylline, isoniazid, alkylating antineoplastic agents, Ciclosporin; Overdose of medication
Metabolic	Renal or hepatic dysfunction, especially rapid changes Hyperammonaemia (35 mM) Na <115 mg/dl (<5 mM) Mg <0.8 mg/dl (<0.3 mM) Ca <5 mg/dl (<1.2 mM) Glucose <36 mg/dl (2.0 mM) or 450 mg/dl (25 mM) associated with keotacidosis
Traumatic	Within <7 d Associated with haemorrhage
Vascular	Subarachnoid bleeding Ischaemic stroke (<7 d) Intracerebral haemorrhage Cerebral vein thrombosis
Withdrawal, deficiency	Alcohol Benzodiazepine Barbiturate Rarely vitamin B12, Vitamin B_6 (young children)
Other	Posterior reversible encephalopathy syndrome Cerebral anoxia Eclampsia Multiple sclerosis within 7 d of relapse
Adapted from [1, 2].	

Table 2: Differential diagnosis of seizures.

Diagnosis	Symptoms
Cardiac events with falls and loss of consciousness	Not necessarily with prodromes, due to cardiac arrhythmia, or carotid sinus hypersensitivity (seealso below under syncope)
Migraine	– Progression of neurologic symptoms >5–15 min followed by headaches (but not always) – Personaland/or family history of migraine – *Basilar migraine:* confusion, bilateral blindness;headache may be minimal or absent
Movementdisorders	– Rare, specific syndrome, like paroxysmaldyskinesia
Psychogenic	– Is not equal to absence of "organic" findings! →positive psychiatric history or findings mandatory – Semiology suggestive of psychogenic onset: eyesclosed, resistant to forceful opening, eye fluttering, rhythmic horizontal head movement, pelvic thrusting – Paradoxical response to antiepileptic drug introduction ("even worse") or no change at all
Syncope	– Brief loss of consciousness, with rapid recovery – Typical prodromes: nausea, "spots before theeyes", sweating, light-headedness, cardiac palpitations – At the end muscle jerks at the end of event,usually less rhythmic, only few ("convulsive syncope"). – Precipitating circumstances often identifiable. Cave in the elderly: recovery may take 10–60 min in elderly, mimickingpostictal state loss of consciousness left often, syncope may presentas transient ischaemic attack (e.g.speech difficulties)
Transient global amnesia	– More often in patients >50 years – Prolonged duration (several hours) without alteration of consciousness; isolated memory deficitexcluding long-term memory before onset of the symptoms
Transientischaemic attack	– More often in patients >50 years – Rather negative symptoms (e.g., weakness,aphasia), but usually no loss of consciousness

Table 3: Conceptual difference between seizures and epilepsy.

Conceptual definition of seizure and epilepsy – 2014 ILAE Annual Report
An epileptic seizure is a transient occurrence of signs and/or symptoms due toabnormal excessive or synchronous neuronalactivity in the brain.
Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences ofthis condition. The definition of epilepsy requires the occurrence of atleast one epileptic seizure
From [4].

Table 4: Reasons of nonresponse to drug therapy (pharmacoresistant epilepsy).

Cause	Recommendation
Patient did not get the right drug	Recording of seizures and work-uphelps todetermine correct epilepsy syndrome
Patientdoes not getenough drug	Determine the blood level of the AEDs, in particular for older AEDs (if possible before drugintake). NB: for most newer drugs there is no linear relationship between blood level and efficacy
Drug is not taken	Determine the blood level of the AEDs, perhaps repeatedly. Ask the patient how many times she/he forgets the AEDs
It is not epilepsy	Recording of habitual events
Epilepsy is not pharmacosensitive	In-patient evaluation in specialized centre: isepilepsy surgery possible?

Why does status epilepticus become super-refractory?

This question is obviously crucial to successful management. It is a standard clinical experience that the more severe the precipitating insult (for instance, in epilepsy after trauma infection or stroke), the more likely is that the status epilepticus to become super- refractory. However, super-refractory epilepsy also occurs frequently in previously healthy patients without obvious cause. In all these cases, the processes that normally terminate seizures have proved insufficient (for review, see Lado and Moshe, 2008). At a cellular level, during a ll|one amongst|one in every of"> one among the foremost interesting recent discoveries has been the popularity that receptors on the surface of axons are in a highly dynamic state, moving onto (externalization), faraway from (internalization) and along the axonal membrane. This 'receptor trafficking' intensifies during epilepsy , and therefore the overall effect may be a reduction within the number of functional -aminobutyric acid (GABA) receptors within the cells affected within the seizure discharge (Arancibia and Kittler, 2009; Smith and Kittler, 2010). As GABA is that the principle inhibitory transmitter, this reduction in GABAergic activity could also be a crucial reason for seizures to become persistent. Furthermore, the amount of glutaminergic receptors at the cell surface increases, and therefore the reduction within the density of the GABA receptors is itself triggered it seems by activation of the glutaminergic receptor systems. Why this could happen is un-known, and from the epilepsy point of view is certainly maladap- tive. This loss of GABAergic receptor density is additionally the likely reason for the increasing ineffectiveness of GABAergic drugs (such as benzodiazepines or barbiturates) in controlling seizures because the status epilepticus becomes prolonged (Macdonald and Kapur, 1999). It has also been repeatedly shown that the extra- cellular ionic environment, which may change in epilepsy , could also be a crucial think about perpetuating seizures, and therefore

the normally inhibitory GABA(A)-mediated currents may become excitatory with changes in extracellular chloride concentrations (Lamsa and Taira, 2003). Other cellular events might also be important. Mitochondrial failure or insufficiency may be one reason for the failure of seizure termination and cellular damage and mitochondrial processes are involved in cell necrosis and apoptosis (Cock et al., 2002). Another category of disease triggering persistent status epilepticus is in- flammatory disease (Tan et al., 2010), and inflammatory processes may be important in the persistence of status epilepticus. The opening of the blood–brain barrier almost certainly plays a serious role within the perpetuation of seizures, thanks to a spread of possible mechanisms (Friedman and Dingledine, 2011), and this may be especially the case in epilepsy thanks to inflammation (Marchi et al., 2011). This may explain the advantages of steroids within the therapy of epilepsy . Leakage of the blood–brain barrier will also lead to higher potassium levels and excitation (David et al., 2009). No genetic mechanism has been identified to elucidate the failure of seizure termination although massive changes in organic phenomenon occur within minutes of the onset of epilepsy . At a systems level, it's been suggested rather fascinatingly and counter intuitively that epilepsy results from a failure to synchronize seizure activity (Schindler et al., 2007a, b; Walker, 2011), which the shortage of synchrony somehow prevents seizure termination. These mechanisms influence strategies for therapy. However, often overriding is that the importance of building explanation for the epilepsy , for emergency therapy directed at the cause could also be crucial in terminating the episode (for review of the influ- ence of aetiology on prognosis, see Neligan and Shorvon, 2011).

Status epilepticus and limbic encephalitis

Status epilepticus and limbic encephalitis The ILAE recently defined epilepsy as: ‘‘a condition resulting either from the failure of the mechanisms respon- sible for seizure termination or from the initiation of mech- anisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which may have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, counting on the sort and duration of seizures’’ [12]. Timepoint t1 is at 5 min after seizure onset, when it is rec- ognized for generalized tonic–clonic status epilepticus that evolution to status is increasingly likely and when treatment should be initiated. T2 is at 30 min, after which there's increasing risk of irreversible consequences. Status is divi- ded along four axes; semiology, aetiology, EEG correlates and age. These axes align with the prognosis of status, which when adequately treated is decided by cause and therefore the age and gender of the patient. The electroclinical state is another prognosticator; subtle status evolving from convulsive status features a particularly poor prognosis. The impressive out-of-hospital randomized, double- blind RAMP ART study has shown that IM midazolam is a minimum of as effective as IV lorazepam within the early treatment of status, in adults and children, probably because IM speed of administration of midazolam compensates for speed of IV distribution of lorazepam. It has long been known that the effect of benzodiazepines in status epilep- ticus wears off very rapidly and it has subsequently been demonstrated that GABAA receptor sensitivity is reduced, sometimes long term. Receptor trafficking may be contributory. As well as a discount in inhibitory neurotransmitters, within 1 h of onset of status in rats, there's a rise in surface NMDA receptors in status, related to increased excitation. Cholin- ergic mechanisms also are implicated, supported by the observation that in pilocarpine induced status epilepticus; the addition of scopolamine provides additional seizure control, when combined with phenobarbital and benzodi- azepines, raising the possibility of the use of drug combi- nations in status. Basic mechanisms are starting to align with clinical evidence in the initial treatment of status with benzodi- azepines, but thereafter the evidence is less clear. Initial uncontrolled reports suggested a 70% success rate for the treatment of status epilepticus with levetiracetam, but a recent randomized controlled trial of out-of-hospital clonazepam plus either levetiracetam or placebo was abandoned due to a scarcity of benefit within the levetiracetam arm. This mirrors the finding that diazepam plus phenytoin confers no additional benefit to lorazepam alone at 12 h and raises questions round the appropriate timing of the addition of AED to benzodiazepines. It also emphasizes the importance of properly controlled studies in a neighborhood where few are undertaken. Shorvon et al. have undertaken meta-analyses of existing therapies. From generally poor quality studies of lacosa- mide, levetiracetam, phenobarbital, phenytoin or valproate in benzodiazepine resistant status, they found efficacy ranging from 50% (phenytoin), to levetiracetam (68.5%), phenobarbital (58–84%) and valproate 76%. Lacosamide treatments were too few to give figures. The conclusion remains that all these drugs may be useful but there is no clear guidance on choice. The caution with which data from uncontrolled studies must be interpreted is high- lighted by a recent randomized study of valproate versus phenobarbital which showed a 44% response to valproate and an 81% response to phenobarbital. However, in chil- dren, valproate may have fewer adverse effects and better efficacy than phenobarbital and similar efficacy to phenytoin. But children might not be like adults with a greater proportion of generalized epilepsies, more aware of valproate. Future options include derivatives of valproate such as valnactomide

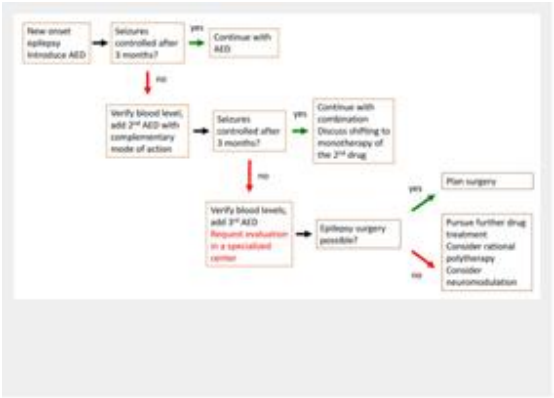
and butyl- propylacetamide, which may be more potently antiepileptic and less teratogenic in animal studies. For status epilepticus which remains refractory to a second line AED, a range of intravenous benzodiazepines or anaesthetic agents may be considered and again Shorvon et al. found that studies are of poor quality. They found that 35% of patients in these studies died and a further 13% had severe neurological deficits and 13% mild neurological deficits on recovery. Studies underway may help answer a number of these questions. Ketamine's role in blocking NMDA receptors has led thereto become increasingly popular within the treatment of refractory status, with some efficacy on the idea of uncontrolled retro- spective series. A randomized trial in children is planned. A recent trial of hypothermia showed no benefit at 90 days . It is increasingly recognized that some patients with refractory status epilepticus, where the cause was previ- ously unrecognized, may be suffering from an antibody mediated encephalopathy, ''limbic encephalitis''

Antiepileptic drugs

Until 1993 only phenobarbital, primidone, phenytoin, car- bamazepine and valproate were available. Of these, only carbamazepine and valproate are still used in a significant number of patients. Today, the administration of phenytoin is limited to difficult cases of status epilepticus, given its availability in an intravenous formulation. Phenytoin is considered neurotoxic and related to cerebellar atrophy and polyneuropathy with chronic treatment. Phenobarbital and primidone are sometimes used in patients with major com- pliance problems, because of their long half-lives. Both drugs frequently lead to vitamin D deficiency and osteo- porosis, so they should be considered as a last resort.

In 2012, Swissmedic issued the recommendation to de- termine HLA-A*3101 before the introduction of car- bamazepine. Studies in northern European and Japanese populations have found an association between Stevens- Johnson syndrome / toxic epidermal necrolysis with car- bamazepine use and the presence of the HLA-A*3101 al- lele. In a southeast Asian population (of Han Chinese descent), these side effects seemed to be related to HLA-B*1502. Oxcarbazepine might also be associ- ated with this risk; however, there is currently insufficient data to support a recommendation for testing the presence of both alleles in patients prior to treatment. There is also ongoing discussion of the cost-benefit of a regular HLA testing, given the high costs of the test, that this complic- ation is extremely rare and that most patients in Switzer- land are clinically monitored by their neurologists or fam- ily doctors.

In 1994 lamotrigine and in 1996 topiramate became avail- able, both with a wide spectrum, for children and as mono- therapy. Lamotrigine is very well tolerated in doses up to 500–700 mg (as monotherapy), and has a favourable ef- fect on mood and cognitive functions. However, it requires very slow introduction extending over 2 months and more, which is not convenient in patients with a high seizure count. Also the high incidence of allergies was an issue during early use of the molecule, but can be largely avoided if this slow titration route is chosen. Topiramate is known for its anorexic effect (noted in around 20% of patients) due to decreased appetite. In some patients and children this can be severe, requiring drug withdrawal. Other side effects are hyperthermia, irritability and depression (which is the reason why it is sometimes used for mania). Rarely, glaucoma or kidney stones are also described. Topiramate probably has teratogenic effects, in particular in polyther- apy. The most teratogenic AED is valproate, and children exposed *in utero* to valproate are at a high risk of major developmental disorders and congenital malforma- tions (10% of cases). In 2015, the Medicines & Healthcare products Regulatory Agency of the UK suggested that val- proate should not be used in female children and young wo- men for this reason, unless other treatments are ineffective or not tolerated .



Before initiating antiepileptic drugs, the underlying syn- drome needs to be determined, usually by a neurologist or neuropaediatrician. Two broad categories are distin- guished: focal epilepsy and genetic (idiopathic) generalised epilepsy. This distinction is important since the latter can significantly worsen if, for example, with carbamazepine, oxcarbazepine or pregabalin are erroneously given. In fact, patients may describe symptoms suggestive of focal epi- lepsy. Work-up with EEG, sleep/long-term EEG and MRI usually helps to differentiate between focal and nonfocal epilepsy.

Fortunately, more antiepileptic drugs became available in Switzerland in the last 10–15 years. However, most of the evidence points to a lack of significantly

augmented ef- ficacy with newer AEDs: the chances of obtaining suffi- cient seizure control remain the same, no matter whether two new or two old AEDs are used. Nevertheless, newer drugs are often better tolerated and therefore should be con- sidered early in the course of the disease in the context of patient-oriented tailored treatment, since this is crucial for the patient's compliance. In table 5, the main features of the drugs are summarised.

II. CONCLUSIONS

With so many new antiepileptic drugs we now have a much larger armamentarium to control seizures. Classical and new antiepileptic drugs differ in their profile of side effects. All are equally effective but some of the new AEDs res- ult in weight loss, pain control or decreased anxiety, which may be welcome properties. Newly developed drugs are generally more expensive than established drugs, and this is also true for AEDs. However, fewer side-effects, few- er pharmacological interactions, long half-life / single daily dose regimen and an easier switch between oral and intra- venous formulations, if available, may argue in favour us- ing new AEDs. The various drugs differ in their mechanisms of action, which should promote research towards a better under- standing of the underlying cellular and molecular mechan- isms. We still need to learn more about "good" polytherapy, i.e., which drug combinations are most efficient. If optimal combinations are known, lengthy trial-and-error treatments with low tolerability are avoided. Super-refractory status epilepticus is a serious condition. The mor- tality rate is substantial, reported in various series between 30 and 50%. Yet, despite the fact that it remains an important clinical problem in all neurology centres worldwide, for many therapies, and treatment approaches, there is a remarkable lack of published data concerning effectiveness, safety or outcome.

Table 5: Summary of antiepileptic drugs

	Lacosamide – Vimpat®	Levetiracetam – several brands	Oxcarbazepine – Trileptal®, Apydan®
Approval in Switzerland	2009	2000	1997
Indication	Add-on in focal seizures ± generalisation (>18 y)	Add-on in focal seizures ± generalisation (>1 month) Monotherapy in focal seizures ± generalisation (>16 y) Monotherapy in IGE with myoclonic seizures (>12 y) Add-on in IGE with tonic-clonic seizures (>12 y)	Monotherapy or add-on therapy in focal onset seizures ± generalisation in adults and children (aged >1 month)
Price for daily dose	9.6 CHF/d at 300 mg/d	1.6 CHF/d at 1000 mg/d	4.2 CHF at 1500 mg/d
Administration	PO, IV	PO, IV	PO
Mode of action	Na⁺-channel blocker, binding CRMP-2	Unknown Suspected release of presynaptic Ca^{++}; enhancement of GABAergic inhibition	Ketc-analogue of CBZ, Blocks voltage gated Na^{+} channels, potentiates K^{+} conduction Inhibits Ca^{++} channels Inhibits NMDA receptors
Frequent adverse effects	Dizziness, fatigue, ataxia, vertigo Rarely: increased PR interval on ECG	Behavioural changes, somnolence,	Hyponatraemia
Oral contraception	No interaction	No interaction	Can lower the contraceptive effect
Other interactions	No interaction	No interaction	OXC level is lowered by PHT, PB, VPA OXC can lower the level of PHT, PB
Remarks			Apydan®: extended version 5 h

	Perampanel Fycompa®	Pregabalin several brands	Rufinamide Inovelon®
Approval in Switzerland Indication	2013 Add-on in focal seizures ± generalisation age (>12 y)	2005 Add-on in focal seizures ± generalisation (>18 y)	2009 Add-on in Lennox-Gastaut syndrome (4 y)
Price for (most frequent) daily dose	8.4 CHF/d at 8 mg/d	4.8 CHF/d at 600 mg/d	18 CHF/d at 2400 mg/d
Administration	PO	PO	PO
Mode of action	Noncompetitive selective AMPA inhibitor of postsynaptic glutamate transmission	Structural derivative of GABA, inhibitor, acts on Ca^{++} channels	Uncertain – reduces Na^{+} channel activity
Frequent adverse effects	Dizziness, somnolence, irritability, headache, ataxia	Weight gain, somnolence, dizziness, irritability	Headache, dizziness, fatigue, nausea, somnolence, diplopia nasopharyngitis, tremor
Oral contraception	Can lower the contraceptive effect	No interaction	Can lower the contraceptive effect
Other interactions	Decreases the level of CBZ, PHT, LTG, midazolam, clobazam etc. Increases the level of OXC. PER level is decreased by >50% in the presence of CBZ, PHT or OXC.	No interaction	Increases VPA and PHT. Level is increased by VPA Level is lowered by CBZ
Remarks		Indication also for neuropathic pain, fibromyalgia, general anxiety	

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBZ = carbamazepine; CRMP-2 = collapsin response mediator protein 2; GABA = gamma-amino butyrate; IGE = idiopathic generalised epilepsy; IV = intravenous administration; LTG = lamotrigine; NMDA = *N*-metnyl-*D*-asparate; OXC = oxcarbazepine; PB = phenobarbital; PER = perampanel; PHT = phenytcin; PO = per os, oral administration; VPA = valproate

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