First-Line Antiepileptic Drugs in Adults: From Guidelines to Personalized Medicine

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Summary

We review in this article the relevant points in the choice and introduction of a first antiepileptic drug (AED). We will present three important aspects regarding that choice: first the guidelines, then the AED characteristics and third some common patient profiles. Although the available guidelines evaluate evidences and provide invaluable information on best tolerated and most efficacious treatments in general scenarios, they have limitations. Given the intensive work they require, they are often not fully up-to-date. Furthermore, they are limited to the inclusion criteria of the corresponding studies, which rarely include patients with significant somatic or psychiatric comorbidities. From a review of the guidelines, we will present the individual characteristics of the AED and how they differ one from the other. We will then discuss frequent and particular clinical situations and emphasize the peculiarities that determine the choice of an AED.

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Antiepileptika erster Wahl bei Erwachsenen: Von Richtlinien zur personalisierten Medizin

Dieser Artikel stellt die notwendigen Konzepte zur Wahl und Einführung eines ersten antiepileptischen Medikaments auf den Prüfstand. Es stehen zwar „Guidelines“ zur Verfügung, welche Evidenzen bewerten und wichtige Informationen über die Therapien mit bester Toleranz und höchster Wirksamkeit in Standardsituationen bieten. Diese unterliegen jedoch Beschränkungen. Angesichts der erforderlichen Arbeit zu deren Ausarbeitung liegen diese nicht immer aktualisiert vor. Darüber hinaus sind sie durch Einschlusskriterien der entsprechenden Studien limitiert, die selten Patienten mit relevanten psychiatrischen oder somatischen Begleiterkrankungen einbeziehen. Nach einer Zusammenfassung der „Guidelines“ führt dieser Artikel die individuellen Eigenschaften jedes Antiepileptikums sowie häufige und spezielle klinische Anwendungssituationen auf. Der Fokus liegt auf den Besonderheiten, welche Wahl und Einführung der Antiepileptika bestimmen.

Schlüsselwörter: Wahl, Begleiterkrankung, Interaktion

Médicaments antiépileptiques de première ligne: des recommandations à la médecine personnalisée

Cet article passe en revue les différents nécessaires aspects pour choisir et introduire un premier médicament anti-épileptique. Des recommandations sont disponibles. Elles résument la littérature et donnent ainsi une information précieuse sur les traitements les mieux tolérés ou les plus efficaces dans des situations générales, mais elles ont des limitations. Au vu du travail nécessaire à leur rédaction, elles ne sont pas toujours complétement à jour. De plus, elles sont restreintes par les critères d’inclusion des études qu’elles analysent, qui intègrent rarement des patients avec d’importantes comorbidités, psychiatriques ou somatiques. Avec les recommandations comme point de départ, cet article présente ensuite les caractéristiques individuelles de chaque anti-épileptique et les situations cliniques fréquentes ou particulières. Un accent est mis sur les particularités qui détermineront ensuite le choix et l’introduction des antiépileptiques.

Mots clés : Choix, comorbidité, interaction

Introduction

The AEDs are symptomatic treatments for epilepsy. The chance for a patient to be seizure free after a first AED is approximately 50% [1]. There are small efficacy variations between AED but the major differences lie in their adverse events profile and pharmacokinetic properties.

Previously, physicians had the choice between 6 “older” AEDs often with a complex hepatic metabolism and high potential for interactions [2]. After 1990, “newer” AEDs have been commercialized, with much simpler pharmacokinetics and less adverse effects, but

with a higher cost. **Table 1** lists a selection of the AEDs that will be cited in this article, sorted by date of introduction.

Clinicians were traditionally more prone to use older AEDs. The trend is now reversing, as illustrated by a British cohort study on more than 60 000 patients [3]: the use of phenytoin (PHT) has decreased from 39.5% in 1993 to 18.3% in 2008. Meanwhile, older generation AEDs are increasingly being replaced by newer AEDs, with lamotrigine (LTG) and levetiracetam (LEV) prescription rates increasing from 2% to 17% and 0 to 8.6%, respectively in the same interval. For those 2 AEDs prescription rates of as much as 30 - 35%, are now reported [4].

To illustrate this review we will consider a fictive case. Mrs G. is a 22-years-old woman and presents with a first unprovoked generalized tonico-clonic seizure. The neurological examination and brain magnetic resonance imaging are normal. The electroencephalogram shows generalized spike and wave discharges. The patient is professionally active, is married, takes oral contraception and is known for a severe anxiety disorder. Taking in consideration of the situation of this fictive patient, we will discuss what is likely to be the best AEDs in this case.

Table 1: Name, abbreviation and date of introduction of selected AEDs. The double line represents the limit between "older" and "newer" AEDs.

Name	Abbreviation	Year of introduction
Phenobarbital	PB	1912
Phenytoin	PHY	1938
Primidone	PRM	1954
Ethosuximide	ESM	1960
Valproic acid	VPA	1967
Carbamazepine	CBZ	1974
Vigabatrin	VGB	1993
Gabapentin	GBP	1993
Lamotrigine	LTG	1995
Topiramate	TPM	1996
Oxcarbazepine	OXC	1998
Levetiractam	LEV	2000
Pregabalin	PGB	2005
Zonisamide	ZNS	2007
Lacosamide	LCM	2009
Perampanel	PER	2013

Overall, we now benefit from the choice of more than 20 drugs. Not every AED is however a good option to start therapy after a first seizure. Several suggestions were made by various neurology or epileptology societies, based on available studies and are published as guidelines. We will briefly review the most widely used guidelines. We will then try to fill the gap between these guidelines and everyday practice by showing individual AED characteristics and how they fit each patient's profile.

Guidelines and illustrative studies

There are several guidelines published in the treatment and diagnosis of epilepsy. A recent review shows that there were at least 35 of them in 2016 [5]. **Table 2** presents treatment recommendations from four important societies: the International League Against Epilepsy (ILAE), the American Academy of Neurology, together with the American Epilepsy Society (AAN/AES), the National Institute for Health and Care Excellence (NICE) and the Société Française de Neurologie (SFN). The differences between guidelines are due to the date of redaction and methodological differences in rating and the evaluation of the available literature [6]. Overall, the guidelines reflect on the increasing place given to newer AEDs over older AEDs. Traditionally, the two "gold standards" were carbamazepine (CBZ) (especially the extended release form) for focal onset seizure and valproate (VPA) for generalized onset seizure. Recent studies have challenged this view. We will now discuss five of these studies [7 - 11] to illustrate this point and understand the rationale of the published guidelines.

The SANAD arm A [8] was an open label multicentre randomized trial with 1700 patients. For the treatment of epilepsy with focal onset seizure, it compared the "gold-standard" CBZ to four newer AEDs: gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC) and topiramate (TPM). In term of retention time (which is influenced by seizure control as well as adverse events), LTG was superior to all the other drugs. The SANAD arm B [9] had a similar design but included patients with generalized onset seizures. VPA was the "challenged" drug against LTG and TPM. In this latter study, VPA showed better efficacy than LTG and better tolerability than TPM. Regarding these results, the authors considered LTG to be the best drug in focal-onset and VPA the best one in generalized-onset seizure (with the exception of women of childbearing age, as discussed below). Although important and well designed, these studies are limited by their open label design and were thus considered "Class III" by the ILAE. A class III study cannot be used to consider a grade A recommendation and this is why LTG is only ranked grade C for the treatment of focal onset seizure in ILAE guidelines.

Brodie et al. [7] have studied LEV in focal epilepsy. They conducted a randomized, double blind, multi-

Table 2: Comparison between four published guidelines. Levels of evidence are expressed using grade A-D or first and second choice for the NICE guidelines. For abbreviations see **Table 1**.

Association	**ILAE**	**AAN/AES**	**NICE**	**SFN**
Guidelines	International	American	British	French
Date (and publication)	Glauser et al. Epilepsia (2006 and 2013)	French et al. Neurology (2004)	*Society website* (2016)	*Society website* (2014)
Sorted by	Grade (A-D)	Grade (A-B)	First (1) or second (2) choice	Grade (A-B)
Comment	Efficacy review (Do not consider itself as a guideline)	Only reviewed **new** AED		
Focal onset seizure	**Adults** A: CBZ, LEV, PHT, ZNS B: VPA C: GBP, LTG, OXC, PB, TPM, VGB D: CZP, PRM **Elderly** A: GBP, LTG, B: - C: CBZ D: TPM, VPA	A/B: GBP, TPM, LTG, OXC	1: CBZ, LTG 2: LEV, OXC, VPA	**General** A/B: CBZ, OXC, LEV, LTG **Elderly** A: LTG
Generalised onset	**Adults** A, B: - C: CBZ, LTG, OXC, PB, PHT, TPM, VPA. D: GBP, LEV, VGB	A/B: -	1: VPA 2: LTG Discuss CBZ and OXC	A: - B: VPA, LTG
Absences	**Children** A: ESM, VPA B: - C: LTG D: -	A: - B: LTG	1: ESM, VPA 2: LTG	A: - B: LTG, VPA
Juvenile Myoclonic Epilepsy	A, B, C: - D: TPM, VPA		1: VPA 2: LEV, LTG, TPM	A: - B: LTG, VPA

centre non-inferiority trial on 579 patients. It showed that LEV was non-inferior to extended-release CBZ in monotherapy. This important trial ranked LEV as grade A recommendation in the ILAE and SNF guidelines. The AAN/AES guidelines were published before this study and therefore they could not include it. The NICE guidelines recommended LEV only as second line treatment because it was not considered cost-effective.

LEV has been further studied in the elderly population. A randomised, double blind retention study from 2015 [11] compared extended-release CBZ, LEV and LTG in this population. LEV was superior to extended-release CBZ. LTG did not differ significantly from the other two drugs. This tends to indicate that the newer AEDs are better candidates AEDs in the elderly, probably because of their relative low propensity of cognitive adverse event and the absence of liver enzyme induction, which can lead to interaction with comedications as discussed below. This is an example of a recent study whose conclusions have not been integrated in guidelines yet. There is also an open label randomized trial of LEV in focal epilepsy, compared with LTG showing no significant difference [10].

In conclusion, guidelines can only bring evidence regarding what questions have been asked in clinical trials, mostly efficacy and to a lesser extend safety of AEDs [6]. A clinician may need more knowledge to choose the appropriate drug for each patient.

Table 3: Important theoretical aspect regarding AED use. SIADH: Syndrome of Inappropriate Anti-diuretic Hormone secretion. For interpretation, see the text.

Name and abbreviation	Spectrum	Elimination (adapt doses)	Pharmacokinetic Specificities.	Useful when...	Avoid when...	Specific sides effects
Valproic acid (VPA)	Broad	Hepatic	Potent liver enzyme inhibitor	Depression Anorexia Migraine	Overweight Essential tremor Pregnancy Osteoporosis	Weight gain Ammonium encephalopathy Polycystic ovary The worst for young woman
Carbamazepine (CBZ)	Narrow	Hepatic	Liver enzyme inducer	Depression Trigeminal neuralgia	Overweight oral contraception Osteoporosis	SIADH Severe skin rash ->see genetic testing
Gabapentin (GBP)	Narrow	Renal	Only renal clearance No interaction	Anxiety Insomnia Neuropathic pain Essential tremor	-	Somnolence
Lamotrigine (LTG)	Broad	Hepatic and renal	Metabolism induced by oral contraception and pregnancy	Depression Anorexia oral contraception Pregnancy Older patients	Insomnia (Myoclonus)	Severe skin rash (especially when rapid introduction with VPA
Topiramate (TPM)	Broad	Renal > hepatic	Liver enzyme inducer (high doses) +/- inhibitor	Overweight Migraine Essential tremor	Depression Anorexia Oral contraception (if >200mg/d) (Pregnancy)	Anorexia Nephrolithiasis Paraesthesia Psychiatric and phasic troubles
Oxcarbazepine (OXC)	Narrow	Hepatic	Liver enzyme inducer (high doses) +/- inhibitor	Depression	Oral contraception Osteoporosis	SIADH (more than CBZ)
Levetiracetam (LEV)	Broad	Renal	Clearance increase during pregnancy +/- oral contraception	oral contraception Pregnancy	Depression Anxiety	Psychiatric troubles (anxiety, irritability, psychosis)
Pregabalin (PGB)	Narrow	Renal	Only renal clearance No interaction	Anxiety Insomnia Restless Legs Neuropathic pain	Overweight	Somnolence Oedema
Zonisamide (ZNS)	Broad	Renal > hepatic	Metabolism inducible	Overweight Oral contraception	Anorexia	Similar to TPM but possibly less psychiatric side effects
Lacosamide (LCM)	Narrow	Hepatic and renal	-	-	-	-
Perampanel (PER)	Narrow (Broad?)	Hepatic	Half-life>48h	-	-	Somnolence +/- irritability

Table 4: Practical information regarding AEDs introduction. This table is only indicative and does not substitute for official information and clinician experience. Average price in 2014, adapted from Rossetti 2015 (Rossetti, Epileptologie, 2015)

Name and abbreviation	Initial Dose	Maximal Dose	Points/potential adverse events to be aware of	Average/month in CHF (dosage)
Valproic acid	2x500mg	3000mg/d	-	20.- (1000mg)
Carbamazepine	2x200mg	1600mg/j	Hyponatremia Skin rash Genetic HLA testing for population at risk (before introduction)	20.- (800mg)
Gabapentin	100mg 3x/j aim: 900-1200mg/d	2400mg/j	-	120.-. (1800mg)
Lamotrigine	1x25mg (12.5 if concomitant VPA)	600mg/d	Skin rash	70.- (200mg)
Topiramate	1x25mg (for 1 week)	200mg/d (400mg/d)	-	55.- (100mg)
Oxcarbazepine	2x150mg	2400mg/d	Hyponatremia	90.- (1200mg)
Levetiractam	2x500mg	3000mg/d	Irritability or psychosis	60.- (1000mg)
Pregabalin	2x75mg	600mg/d	-	120.- (300mg)
Zonisamide	1x50mg (for 1 week)	400mg/d	-	115.- (200mg)
Lacosamide	2x50mg (1x50mg)	400mg/d	-	160.- (200mg)
Perampanel	1x2mg	8-12mg/d	-	250.- (6mg)

Beyond guidelines: tailoring the treatment according to the patient's needs

As pointed out above, guidelines reflected on the trials that assessed these medications. People included in trials are chosen in order to demonstrate a difference between the two arms of the studies. The results are difficult to extrapolate to clinical practice as these studies are limited by their short duration, rigid inclusion and exclusion criteria, inability to analyse the effect of concomitant medications, and lack of dosing flexibility. Regulatory AED trials often ignore aetiology and epilepsy syndrome which may affect prognosis, and also include homogenous cohorts with a high seizure frequency, without major comorbidities [12]. In order not to worsen any concomittant condition or to interfere with other treatment, it is important to consider the overall situation of the patient before starting a AED. Furthermore, AEDs can be chosen to help to improve the symptoms of another condition, such as mood disorder, neurogenic pain, or insomnia. **Tables 3** and **4** summarize important aspects in the choice of the first line AED listing 11 of the most common ones. Beyond the most relevant AEDs from the guidelines, this table adds two of the latest AEDs lacosamide (LCM) and perampanel (PER), whose prescription rate is likely to be growing in everyday practice (e. g. LCM has been approved for monotherapy in the USA in 2014). We did not however include retigabine (as its discontinuation was recently announced), nor PHT or phenobarbital (PB) (due to their adverse events and pharmacokinetic, these medications are usually not suitable first-line drugs nowadays). For **Table 3**, each column presents informations with clinical implications. Broad spectrum AED are used in case of generalized onset seizures, although the underlying level of evidence is weak, as underlined in the guidelines. A recent evidence review [13] has supported the use of just 5 AEDs for the treatment of primarily generalized convulsive seizures: LTG, LEV, TPM, VPA, with evidence for ZNS considered low-level. Of these, only LTG, LEV, and TPM have demonstrated efficacy in randomized, double blind, placebo-controlled trials of adjunctive treatment for drug-resistant generalised onset seizures. A recent study also suggests that PER could be used in that context [14]. The next column shows clearance mechanisms and pharmacokinetic properties that have to be taken into consideration in case of renal or hepatic failure. Drugs with pure hepatic metabolism are also more prone to lead to interaction. The three last columns are important for a tailored AED choice regarding each patient. It presents the effects of the different AEDs in conditions other than epilepsy. **Table 4** shows practical data: proposed initial and usually maximal dosage, recommended controls and average monthly prices.

The titration and dosing schema is another important aspect of the choice of first line AEDs. The speed of titration needed is usually dictated by the activity of the disease. A medication whose titration to reach efficient level takes weeks (such as LTG) is inadequate to control an epilepsy with daily disabling seizures. Similarly, the availability of an intravenous formation (such as LEV, LCM) also allows, most often with a loading bolus, to obtain quickly efficient medication levels. On the other side, titration pace is likely to be slowed down in patients reporting frequent medication intolerance. The dosing can also be determinant, for instance to improve compliance with AEDs requiring only one daily dosing (ZNS for instance) [15]. The first-line medication is then titrated according to the response (control of seizure) and tolerance. If the control is insufficient, it has been suggested at times to increase the dosage until signs of intolerance appear. Remission, which is the aim of a first line treatment, is however likely to occur at relatively low dosage [16], making inappropriate an indiscriminate continuous dosage increase if no effect on seizures is observed.

We will now discuss several common situations: elderly patients, patients with neoplasm or HIV infection, women in child bearing age, patients with intellectual disability and CBZ genetic testing.

Specific populations

The most relevant aspects of elderly patients are comorbidities (leading to frequent comedications) and often reduced renal and hepatic functions [11]. Regarding this aspect, drugs with simpler pharmacokinetic and without liver enzyme induction action (non-"inducers") should be preferred, as illustrated in the above-mentioned guidelines. Osteoporosis is often present in older patients and can also be worsened by inducers. Those patients are also more liable to cognitive adverse effects of medication. In this population, LEV, LTG, or PGB, are good candidates AEDs.

Patients with primary brain tumor, metastases or cancer in general are at increased risk of seizure and often need both AED and chemotherapy. Liver enzyme induction is also problematic in this case: CBZ, PHT, PB and primidone (PRM) can decrease the efficacy of the chemotherapy agent. VPA has a possible direct beneficial effect against glial cell tumor but this has not yet been proven in prospective trials [17]. Meanwhile, VPA can also lead to increased chemotherapy serum concentration possibly leading to toxicity, because of its action as liver enzyme inhibitor [18]. The same rule applies for HIV-infected patients taking antiviral agents, as induction by AEDs can lead to failure of antiretroviral treatment. Some antiretroviral treatments can also interfere with metabolism of some AEDs (mostly CBZ). The AAN issued guidelines regarding treatment adjustment in this case [19].

It is the general consensus to continue AEDs during pregnancy because of the potentially severe consequences of recurrent seizures for the mother and the

foetus [20]. Indeed, the consequences of uncontrolled seizures are considered to outweigh the risk of medication. Overall, children of mothers with epilepsy taking AEDs are at increased risk of major foetal malformations (approximately 3 - 7% compared to 2% in the general population) [21, 20], but important differences exist between AEDs [22]. The AEDs with the best profile in this situation are LTG, LEV, CBZ, and OXC. The worst AED in pregnancy is by far VPA. It causes a malformation risk of 6% for doses <700 mg and up to 25% for doses >1500 mg. Beyond this risk, there are also cognitive and developmental complications for the child after its exposition. In child bearing age women, VPA should be reserved to patients not responding to other treatment option. LTG and LEV are safe AEDs in pregnancy, although they undergo a change in their metabolism during pregnancy and their serum level needs to be followed, to adapt the dosage accordingly.

Regarding contraception, liver enzyme inducers AEDs again are better avoided because they can lead to loss of efficacy of contraceptive pills. The alternative is to use highly dosed contraceptive pills. Conversely, the oral contraception can induce the metabolism of LTG which may also justify dosage adaptation.

Epilepsy is more prevalent in people with intellectual disabilities, with prevalence rates of up to 50% in severely disabled institutionalized patients [23]. The seizures are often intractable and the management of adverse events can be complicated by comorbidities and communication difficulties. The aim of the treatment should be not to worsen cognition or motor skills as well as to avoid to induce behavioural difficulties. Among AEDs, the newer ones probably have good efficacy and tolerance, as illustrated by a prospective study showing a high 3-year retention of approximately 70% for LTG [23].

CBZ (more than LTG) is associated with skin hypersensitivity reactions in up to 10% of patients. Most are erythematous maculopapular rash. However, in rarer cases (1-10/10 000) much more severe reactions can happen such as Steven Johnson syndrome or toxic epidermal necrolysis. These complications are potentially very severe and are associated with genetic susceptibility in HLA variants HLA-B*15:02 and HLA-A*31:01, which have different prevalence according to patient's origin. While European Medicines Agency and the American Food and Drug Administration require the search for HLA-B*15:02 before instituting CBZ in people with Asian ancestry (descendant of Chinese, Thai, Indian, Malay, Filipino, Indonesian; level A), they are not taking position on systematic testing for HLA-A*31:01. The level of evidence was recently reviewed [24] with the following recommendation: preventive genetic testing for HLA-B*15:02 for patients at risk of having this variant, but also possibly for general population (level C). Testing of HLA-A*31:01 is recommended for all patients regardless of origin (level B) in this review, although the benefit of testing this HLA variant is less clear. Swissmedic also supports the testing for HLA-A*31:01 in Caucasians. The Swiss League Against Epilepsy issued a statement, currently in press, putting these recommendations in perspective. It is not the point of this article to argue with the regulatory authorities recommendations, but the potential necessity of genetic testing before introducing CBZ led in practice to a decrease of its use.

Conclusion

Back to the treatment of Mrs G. The first aspect is that she has epilepsy with generalized onset seizure, for which, the level of evidence for the choice of treatment is low. Five AEDs have a broad spectrum of action: VPA, LTG, TPM, LEV and ZNS. Although probably the most efficient, VPA is not a good option regarding the fact that this patient is in childbearing age. The often prescribed LEV can worsen the anxiety disorders and should also be avoided. LTG is a good option because it has favourable effect on mood disorders and it is a safe option for pregnancy. It is compatible with contraception or pregnancy although doses have to be adapted.

In conclusion, it is essential to consider the patient globally when choosing the first AED, in order to maximise the chances of achieving remission as quickly as possible without significant adverse events.

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