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Summary

Since the last 20 years, more than 12 new antiepileptic drugs (AEDs) have been introduced on the market. Several randomized controlled trials confirmed the efficacy of these newer AEDs as add-on for polytherapy or (less frequently) as monotherapy in patients with epilepsy. However, about one third of patients still do not achieve sustained seizure control, creating the need to further generate novel AEDs with novel acting mechanisms and routes of administration, and to develop disease-modifying drugs.

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Key words: Epilepsy, medical treatment, AED

Der Vorzug „neuer“ versus „alter“ Antiepileptika: Wo liegt die Evidenz?

In den letzten 20 Jahren sind mehr als 12 Antiepileptika auf dem Markt eingeführt worden. Mehrere randomiserte Studien haben die Wirksamkeit dieser neuen Substanzen als zusätzliche Mittel oder (seltener) als Monotherapie der Epilepsie bestätigt. Trotzdem haben weiterhin etwa ein Drittel der Patienten unkontrollierte Anfälle; deswegen sind weitere Antiepileptika mit innovativen Verabreichungsmethoden und Wirkungsmechanismen, als auch mit Krankheit-beeinflussenden Eigenschaften, dringend benötigt.

Schlüsselwörter: Neue Antiepileptika, randomisierte Studien, Evidenz-basierte Medizin

Choix des nouveaux antiépileptiques par rapport aux anciens : où est l‘évidence ?

Lors des 20 dernières années, plus de 12 nouveaux médicaments antiépileptiques ont été introduits sur le marché. Plusieurs essais randomisés ont prouvé l’efficacité de ces substances en tant que « add-on » avec d’autres antiépileptiques, voir même (plus rarement) comme monothérapies. Cependant, environ un tiers des personnes avec épilepsie reste pharmacorésistante ; cet aspect illustre le besoin impérieux de développer de nouveaux moyens pharmacologiques avec des mécanismes d’action et modes d’administration innovatifs, ainsi qu’avec des propriétés pouvant influencer la maladie épileptique.

Mots clés : Epilepsie, traitement médical, MAE

Scelta dei nuovi antiepilettici: dov‘è l‘evidenza?

Negli ultimi 20 anni sono stati introdotti sul mercato più di 12 nuovi medicamenti antiepilettici. Diversi studi randomizzati ne hanno dimostrato l’efficacia, soprattutto come “add-on” in politerapia, molto meno frequentemente come monoterapia. Purtroppo un terzo delle persone che vivono con l’epilessia continua comunque ad essere farmacoresistente; questo aspetto dimostra chiaramente il bisogno interrogabile di sviluppare nuovi mezzi farmacologici con meccanismi d’azione innovativi, che permettano vie d’amministrazione alternative, e – non da ultimo – con proprietà che possano influenzare l’epilettogenicità.

Parole chiave: Epilessia, trattamento, MAE

Background

Epilepsy is a heterogeneous brain disorder with an annual incidence between 50 and 120 per 100 000 and a prevalence of around 700 per 100 000 [1]. Hence, epilepsy is one of the most common serious neurological disorders, and the burden of disease is comparable with lung cancer, and breast cancer in women [2]. Moreover, epilepsy is associated with other comorbidities, including depression, anxiety, increased morbidity and mortality, seizure-related falls and injuries, and psychosocial stigmatization. Pharmacological therapy with antiepileptic drugs (AEDs) constitutes the backbone of the treatment of epilepsy. About two thirds of adults with newly diagnosed epilepsy will achieve sustained seizure control while taking AEDs [3]. However, approximately half of these patients experience mild to moderate adverse events (AEs) under medical treatment [4, 5]. Moreover, drug resistant epilepsy occurs in 20-30%

of patients with newly diagnosed epilepsy. The choice of drug is primarily based on evidence of efficacy and effectiveness for the respective patient´s seizure type or epilepsy syndrome and by tolerability considerations. For the optimum selection of these drugs, other patient-specific variables have to be considered, including age, gender, comorbidities, drug-drug interactions, childbearing potential or intellectual impairment. The „ideal AED" should have broad spectrum efficacy, provide sustained seizure control, be well tolerated without any safety concerns, be easy to take, and be available in several formulations.

Currently, more than 20 classical (so called „older") and newer AEDs are available to treat epilepsy in adults, with each drug having its potential advantages and disadvantages (**Table 1**).

This review will focus on the body of evidence on the use of newer versus older AEDs in the treatment of epilepsy.

Body of Evidence

Monotherapy

In 2006, the International League Against Epilepsy (ILAE) report provided an evidence-based analysis of AED efficacy / effectiveness as initial monotherapy for epileptic seizures and syndromes, including 50 randomized controlled trials (RCTs) and seven metaanalyses [6]. A very recent update of this review identified additional three class I and 11 class III studies since 2005 [7]. The combined analysis now encompasses a total of 64 trials (class I evidence in 7, class II evidence in 2) and 11 metaanalyses. The clinical trial rating has been related to distinct levels of evidence (**Table 2**).

The authors concluded that there are major methodological weaknesses in the quality of available evidence, especially there is a lack of adequately designed RCTs for patients with generalized seizures/epilepsies, and in children. Many RCTs cannot answer crucial clinical questions creating a need for additional multicenter clinically relevant RCTs answering the unmet questions.

Additional evidence

A recent randomized, open-label, controlled, parallel group, multicenter trial was conducted to test the superiority of the LEV over the LTG as initial monotherapy for epilepsy [8]. The primary endpoint was the rate of seizure-controlled patients in the first 6 weeks. Furthermore, efficacy, tolerability and quality of life were evaluated. Six weeks after randomisation the proportions of seizure-controlled patients were 67.5% (LEV) versus 64.0% (LTG) (p=0.47). Adverse events occurred in 74.5% (LEV) versus 70.6% (LTG) of the patients (p=0.38). There were no significant differences with regard to efficacy and tolerability of LEV and LTG in newly diagnosed focal and generalised epilepsy. Another unblinded randomized study compared the effectiveness of levetiracetam (LEV) with controlled release carbamazepine (CBZ-CR) as monotherapy for focal seizures or extended release valproate (VPA-ER) for generalized seizures in patients with newly diagnosed epilepsy [9]. The hazard ratio for time to treatment withdrawal was 1.02 (0.74 to 1.41) for LEV compared to VPA-ER and 0.84 (0.66 to 1.07) for LEV compared to CBZ-CR. Similar proportions of patients within each treatment arm reported at least one adverse event: 66.1% LEV versus 62.0% VPA-ER; 73.4% LEV versus 72.5% CBZ-CR. The authors concluded that LEV monotherapy was not superior to CBZ-CR/VPA-CR in terms of global outcome.

Drug resistant epilepsy

The clinical comparability of new AEDs in partial refractory epilepsy was evaluated including 62 placebo-controlled, and eight head-to-head RCTs [10]. A random-effect metaanalysis was used to derive pooled estimates of odds ratios (OR) and number needed to treat / harm (NNT/NNH). Indirect comparisons of responder rate based on relative measurements of treatment effect (ORs) favored topiramate (1.52; 1.06-2.20) in comparison to all other AEDs, whereas gabapentin (0.67; 0.46-0.97) and lacosamide (0.66; 0.48-0.92) were less efficacious, without significant heterogeneity. Topiramate and levetiracetam were more efficacious, whereas gabapentin and tiagabine were less efficacious when analyses were based on absolute estimates (NNTs). Withdrawal rate was higher with oxcarbazepine (OR 1.60; 1.12-2.29) and topiramate (OR 1.68; 1.07-2.63), and lower with gabapentin (OR 0.65; 0.42-1.00) and levetiracetam (OR 0.62; 0.43-0.89). The authors pointed out that the differences were too small to derive any conclusions about which new AED(s) has superior effectiveness. Moreover, a recent metaanalysis of 54 randomized controlled add-on studies in patients with drug resistant epilepsy elucidated a benefit in efficacy between add-on treatment with a new AEDs versus add-on treatment with placebo in only 6% for seizure freedom and 21% for a 50% reduction in seizure frequency, suggesting a need for developing more effective AEDs for drug resistant epilepsy [11].

Despite the introduction of more than 12 new AEDs over the past 20 years, there is limited evidence supporting better outcomes for people with epilepsy. In a recent study performed in Scotland, the proportion of patients achieving seizure freedom rose only from 64% to 68% with the use of new AEDs [12].

Table 1: Overview of available antiepileptic drugs.

Drug (year of first approval)	Mechanism of	Potential advantages	Potential disadvantages
Older antiepileptic drugs			
Bromide (1857)	GABA potentiation	Broad spectrum action	CNS-related AEs, acneiform rashes, loss of appetite
Carbamazepine (1964)	Na^+ channel blockade	Highly effective, extensively studied	CNS related AEs, rash, hyponatriaemia, enzyme induction, osteoporosis, leucopenia
Phenobarbital (1912)	GABA potentiation	Broad spectrum action, once daily, attractive costs	CNS related AEs, rash, osteoporosis, enzyme induction, folate deficiency, enzyme induction, Dupuytren's contractures, hematological toxicity
Ethosuximide (1958)	Calcium channel blockade (T-type)	Well proven in childhood absence epilepsy	Gastrointestinal and CNS-related AEs, idiosyncratic reactions, narrow spectrum efficacy
Phenytoin (1938)	Na^+ channel blockade	Rapid titration, intravenous formulation available, attractive costs	CNS-related AEs, gingival hyperplasia, hirsutism, osteoporosis, enzym induction, idiosyncratic reactions
Valproate (1967)	Multiple (GABA potentiation, NMDA inhibition, sodium channel and calcium channel blockade (T-type))	Broad spectrum action, rapid titration, few interactions, intravenous formulation available	Hair loss, weight gain, gastrointestinal AEs, teratogenicity, hepato-toxicity, hyperammonemia, thrombocytopenia, extrapyramidal symptoms
Newer antiepileptic drugs			
Eslicarbazepine (2009)	Na^+ channel blockade	Once daily	CNS-related AEs, rash, hyponatraemia, interaction with combined oral contraceptives
Felbamate (1993)	NMDA inhibiton	Broad spectrum action	CNS-related AEs, aplastic anemia, fulminate hepatic failure, weight loss, interaction with combined oral contraceptives, last-resort drug
Gabapentin (1993)	Calcium channel blockade	Low risk of allergic reactions, Low risk of drug interaction, good tolerability	Mild CNS-related AEs, weight gain
Lacosamide (2008)	Enhanced slow inactivation of voltage-gated Na^+ channels	Low risk of drug interaction, intravenous formulation available	CNS-related AEs, nausea

Table 1: Overview of available antiepileptic drugs.

Drug (year of first approval)	Mechanism of	Potential advantages	Potential disadvantages
Lamotrigine (1990)	Na^+ channel blockade	Broad spectrum action, few interactions, good tolerability	CNS-related AEs, rash, hypersensitivity reactions, interaction with combined oral contraceptives
Levetiracetam (2000)	SV2A modulation	Broad spectrum action, intravenous formulation available, low risk of drug interaction	CNS-related AEs, neuropsychiatric and behavioural effects
Oxcarbazepine (1990)	Na^+ channel blockade	Good tolerability	CNS-related AEs, rash, hyponatraemia, interaction with combined oral contraceptives
Perampanel (2012)	AMPA antagonist	Novel mechanism of action, once daily	CNS-related AEs, neuropsychiatric and behavioural effects
Pregabalin (2004)	Calcium blockade	Low risk of allergic reactions, low risk of drug interaction	CNS-related AEs, weight gain
Retigabine (2011)	K^+ channel opener	Novel mechanism of action	Urinary retention, CNS-related AEs, blue skin discoloration and retinal pigmentary changes, retinal dystrophy, last-resort drug
Rufinamide (2004)	Na^+ channel blockade	Orphan drug for Lennox-Gastaut syndrome	CNS-related and gastrointestinal AEs
Stiripentol (2007)	GABA potentiation	Dravet Syndrome in children	Drowsiness, hyperactivity, weiht loss, dystonia, ataxia, tremor, enzyme inhibitor
Topiramate (1995)	Multiple (GABA potentiation, AMPA inhibition, sodium and calcium channel blockade)	Broad spectrum action	CNS-related AEs, paraesthesia, fatigue, weight loss, renal stones, neuropsychiatric effects, interaction with combined oral contraceptives
Vigabatrin (1989)	GABA potentiation	Well proven efficacy in infantile spasms in tuberous sclerosis	CNS-related AEs, irreversible concentric visual field deficits, last-resort drug
Zonisamide (2000)	Na^+ channel blockade	Broad spectrum action	CNS-related AEs, anorexia, weight loss, renal stones, rash, neuropsychiatric effects

AEs : adverse events

Table 2: Level of evidence for particular seizure types and epilepsy syndromes (adapted from [7]). Of note, these ratings may differ from common clinical practice.

Seizure type/epilepsy syndrome	Level of evidence (efficacy/effectiveness of AED)
Partial onset seizures (adults)	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXc, PB, TPM, VGB Level D: CLZ, PRM
Partial onset seizures (children)	Level A: OXC Level B: none Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB,CLZ,LTG, ZNS
Partial onset seizures (elderly)	Level A: GBP, LTG Level B: none Level C: CBZ Level D: TPM, VPA
Generalized tonic-clonic seizures (adults)	Level A: none Level B: none Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Generalized tonic-clonic seizures (children)	Level A: none Level B: none Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Absence seizures (children)	Level A: ESM, VPA Level B: none Level C: LTG Level D: none
Benign epilepsy with centrotemporal spikes	Level A: none Level B: none Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy	Level A: none Level B: none Level C: none Level D: TPM, VPA

Clarifications of terms: Level A: ≥ 1 Class I studies, or metaanalysis meeting class I criteria sources, or ≥ 2 Class II studies; Level B: 1 Class II study, or metaanalysis meeting class II criteria; Level C: ≥ 2 Class II double-blind or open-label studies; Level D: 1 Class III double-blind or open-label study or ≥ 1 class IV clinical studies or data from expert committee reports, or opinions from experienced clinicians.

Further Considerations

Women with childbearing potential

If clinically possible, AEDs known to be associated with congenital malformations in offspring of women with epilepsy, including valproic acid, as well as a combination of AEDs, should be avoided during pregnancy, especially during the first trimester. The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) reported the lowest malformation rates with lamotrigine < 300mg/day, or carbamazepine < 400mg/day compared with valproic acid and phenobarbital at all doses and with carbamazepine ≥ 400mg/day [13]. A recent guideline for treatment of women with epilepsy further suggested that intrauterine exposure to valproic acid, phenytoin and phenobarbital reduces cognitive outcomes in offspring and should therefore be avoided [14]. Moreover, very recently the EMA's Pharmacovigilance and Risk Assessment Committee (PRAC) has further recommended strengthening the restrictions on the use of valproate in women with childbearing potential due to the above mentioned risk of malformations and developmental problems in children exposed to valproate in uterus [15]. Lamotrigine is an appropriate choice, although it might be less efficacious than valproic acid [5].

Elderly people

Aging is associated with changes in pharmacokinetics and pharmacodynamics, implying a more cautious choice of drugs and dosing regimen in elderly patients with epilepsy. Additionally, concomitant internistic diseases including hypertension, renal insufficiency and cardiovascular problems, are common and require further medical treatment. The likelihood of drug interactions is increasing and therefore, monotherapy with a well tolerated drug without the potential of drug-drug interactions is aimed. Although class I evidence is lacking, gabapentin and lamotrigine, as well as topiramate and levetiracetam, might be appropriate choices [16 -19]. Furthermore, an easy-to-use drug is preferable due to probable cognitive impairment resulting in potential non-adherence.

Comorbidities

For the optimum choice of AED treatment, comorbidities have to be taken into consideration. Psychiatric comorbidities, especially depression and generalized anxiety disorders are very common in patients with epilepsy. Lamotrigine is beneficial in bipolar depression, valproic acid and carbamazepine are used as mood stabilizer [20] and pregabalin is appropriate in patients with coexisting generalized anxiety disorder [21]. A recent special report on antiepileptic drugs and suicidality pointed out that although some (but not all) AEDs can be associated with treatment-emergent psychiatric problems possibly leading to suicidal ideation and behavior, the actual suicidal risk is yet to be established, but it seems to be very low [22]. Clinicians should be aware of risk factors and if necessary, patients should be referred for a psychiatric evaluation, but AED treatment should not be withheld, even in subjects with suicidal risks. Not least, pregabalin is well-studied for the treatment of neuropathic pain [23], and valproic acid and topiramate are effective in migraine prophylaxis, respectively [24].

Formulations

Intravenous loading doses, if needed, can be given with older AEDs, including valproic acid, and phenytoin, and newer AEDs such as levetiracetam and lacosamide. Both of the newer AEDs have the advantage of a favorable tolerability profile without sedation, cardiovascular adverse events, or toxic local effects.

Enzyme induction / inhibition

A main advantage for many of the newer AEDs, especially gabapentin, pregabalin, lamotrigine, levetiracetam and lacosamide, is that they do not induce or inhibit hepatic enzyme function (see **Table 1**). This clearly reduces the potential for drug-drug inter-action which is particularly favorable for patients taking non-AED drugs or AED polytherapy.

Conclusion

Several randomized, double-blind, controlled trials confirm the efficacy of new AEDs in monotherapy and polytherapy [7, 10]. However, no class I evidence has demonstrated superior efficacy/tolerability for any specific AED for treating drug resistant epilepsy. Compared with classical AEDs, some of the newer drugs offer the advantage of not affecting the hepatic enzyme function (GBP, PRG,LTG, LEV, LCM) , rapid onset of action (GBP, OXC, LEV and LCM), intravenous loading (LEV and LCM), broad spectrum efficacy (LTG, TPM, ZNS and LEV) or use for treating comorbidities.

The fact that over one third of patients with epilepsy still do not achieve seizure freedom with available AEDs gives rise to further research with a view to develop AEDs with novel mecanisms of action and novel modes of administrations. The novel generation of AEDs has certainly expanded the treatment options; however, these drugs neither reduce the prevalence of drug resistant epilepsy, nor prevent the development of epilepsy in patients at high risk.

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