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A Clinical Overview of the New Antiepileptic Drugs

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Over the past decade, several new antiepileptic drugs (AEDs) have become available including Gabapentin, Lamotrigine, Topiramate, Tiagabine, Oxcarbazepine, Levetiracetam, Zonisamide, Vigabatrin and Felbamate. These drugs had proved their efficacy in various types of seizures. Lamotrigine and Topiramate were suggeseted as effective for use as monotherapy for generalized seizures, and Topiramate, Lamotrigine, Oxcarbazepine and Gabapentin for partial onset seizures, and Vigabatrin for infantile spasms. All the new anti-epileptic drugs are also effective as add-on therapy for partial seizures without or with secondary generalization.

This article briefly reviews the pharmacodynamics of the new antiepileptic drugs to provide information that physicians in the Kingdom particularly non-epileptologists for rational choice and judicious use of these agents.

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Epilepsy is one of the most common neurological disorders with reported prevalence of 6-8/100,000 incidence of 30-50/100,000 per year and cumulative incidence of 3%. It requires prolonged and sometimes life-long drug therapy[1]. Available anti-epileptic drugs are categorized into three major groups: conventional anti-epileptic drugs approved before 1990; new antiepileptic drugs approved after 1990 and unconventional antiepileptic drugs that are not normally used to treat seizures or may have serious side effects (Table 1)[2]. Although the new antiepileptic drugs (AEDs) are already in use in the United States, Europe and Japan, only six (Gabapentin, Lamotrigine, Vigabatrin, Topiramate, Oxcarbazepine, and Levetiracetam) of them are currently available in the Kingdom. Selecting the best drug for a particular patient and for specific seizure type can be confusing for the physician sometimes and patients may even solicit these medications from abroad. A review of the pharmacology, pharmacokinetics, indications and side effects of these new anti-epileptic drugs with the current understanding of their various clinical profiles is therefore required to provide their judicious use locally.

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Development of antiepileptic drugs; the advantages and limitation

The new antiepileptic drugs (AEDs) have been tested at the pre-clinical phase with pharmaco-resistant forms of epilepsies in animals that does not faithfully represent the pathological, clinical or electrical models of the human disease[3]. In the clinical phase, the new anti-epileptic drugs have been tested mainly as an add-on therapy in patients with partial seizures with or without secondary generalizations who fail to respond to conventional anti-epileptic therapy or prior to surgical therapy[4]. The number of controlled trials on any of the AED is small for the idiopathic forms of epilepsy. And even some guidelines concluded that the difference in efficacy between the conventional and the new AEDs is not significant[5,6].

The New antiepileptic Drugs

Gabapentin (NEURONTIN) is a structural analogue of gamma- aminobutyric acid (GABA) which does not interact with either $GABA_A$ or $GABA_B$ receptors, convert to GABA or GABA agonist nor does it inhibit GABA up-take or degeneration[7]. Although its mechanism of action is unknown, it may increase the total central nervous system level of GABA[8]. It has been shown to be effective in complex partial seizures with or without secondary generalization and generalized tonic-clonic seizures with no significant effect compared to placebo in reducing the frequency of myoclonic seizures or absences, and may occasionally aggravate typical absences[9-12]. Gabapentin is well absorb from the gastrointestinal tract which makes its bioviability non-dose dependent, has a half life ($t_{1/2}$) of 6 hours, is eliminated by renal excretion unchanged and is well tolerated[13,14]. The commonest side effect is fatigue and weight gain.

Lamotrigine (LAMICTAL) acts by inhibiting the release of excitatory amino acids such as glutamate through the modulation of sodium and calcium channels[15]. And lamotrigine is effective as an add-on or monotherapy for patients with partial seizures with or without secondary generalization, and in addition, in the treatment of absence, myoclonic seizures, and other seizure types associated with Lennox-Gastaut syndrome[16,17]. Lamotrigine is partially protein bound and may have significant drug interactions with Valproic acid, Garbamazepine, Phenytoin and Phenobarbitone because of its glucoronodization in the liver[18]. It significantly alters plasma concentration of other AEDs when given concurrently, and its most significant side effect is a hypersensitivity reaction with skin rash that occurs usually within the first three months of therapy[19]. Slow introduction of Lamotrigine may offset this complication. The occurrence of a previous rash with other anti-epileptic drug, particularly Carbamazepine is a good predictor of Lamotrigine skin hypersensitivity reaction.

Vigabatrin (SABRIL) is a synthetic GABA derivative which causes irreversible inhibition of GABA transaminase thereby increasing the pool of the inhibitory neurotransmitter[20]. It is well absorbed following an oral dose and is principally eliminated by the kidneys[21]. It binds to protein, however has $t_{1/2}$ of 5 hours and is not

metabolized in the liver. It has a limited antiepileptic spectrum however and is particularly effective in patients with Lennox-Gastaut syndrome[22]. Its main side effects are visual field defects, weight gain and ataxia and may also exacerbate pre-existing depression[23].

Topiramate (TOPAMAX) is a sulfamate-substituted monosacharide with carbonic anhydrase inhibitory properties. The mechanism of action as an antiepileptic drug is related to inhibition of $GABA_A$ receptor mediated activities and its direct modulating effect is independent of carbonic anhydrase inhibition[24, 25]. It is well-absorbed given orally with a plasma $t_{1/2}$ of approximately 24 hours. It has minimal protein binding properties and is eliminated principally by the kidneys and to a lesser extent by the liver[26]. Topiramate increases the serum levels of Phenytoin and reduces that of Valproic acid[19]. Topiramate is effective in primary generalized epilepsies and partial seizures with or without secondary generalization[26,27]. The commonest side effect include fatigue, weight loss, renal stones and psychological disturbances[28].

Tiagabine (GABATRIL) exhibits its epileptic activity through selective GABA re-uptake inhibition[29]. It is well-absorbed following an oral dose; is highly protein bound, eliminated primarily by the liver and has $t_{1/2}$ of approximately 6 hours[30]. It increases the serum levels of Phenytoin and Valproic acid and is effective as an add-on therapy in patients with partial seizures with or without secondary generalization[18]. The main side effects include light headedness, asthenia, somnolence, tremor, and non-convulsive status epilepticus[31].

Levetiracetam (KEPPRA) has a novel binding site (90K da binding site) which is the synaptic vesicle protein (SV2A) present in synaptic vesicles and some neuroendocrine cells[32]. Its mechanism of action is distinct from that of other anti-epileptic drugs[33]. Levetriacetam is well-absorbed following an oral dose, 66% of it is eliminated unchanged in urine, and it does not cause hepatic enzyme induction. Levetriacetam is effective in patients with partial seizures with or without secondary generalization and the main side effects include behavioural disturbances which may necessitate discontinuation[34, 35].

Zonisamide (ZONEGRAN) exerts its antiepileptic activity by blocking voltage-sensitive sodium and voltage-dependent calcium channels, enhances GABA release, blocks the potassium glutamate response and reduces glutamate-mediated synaptic excitation[36]. In addition, it scavenges nitric acid and other free radicals and inhibits lipid peroxidation and free radical-induced DNA damage thereby protecting neurons from further damage and it also stabilizes the neuronal membrane[17]. Zonisamide is well-absorbed following oral administration and eliminated unchanged by the kidneys. Its $t_{1/2}$ ranges from 50-70 hours[2]. Zonisamide is effective as an add-on therapy in generalized seizures and partial seizures with or without secondary generalization; the main side effects include somnolence, dizziness and nephrolithiasis[38]. The side effects can be minimized by slow titration, adequate hydration and avoiding exposure to excessive temperatures.

Oxcarbazepine (TRILEPTAL) and its active metabolite (10 monohydroxy epoxide derivative) block voltage dependent sodium and voltage-activated calcium channels[39]. It is distributed throughout tissue and eliminated by the liver. Oxcarbazepine is similar to carbamazepine in its spectrum of anti-convulsant activity. It is currently recommended as either a first line monotherapy or an add-on therapy for partial seizures with or without secondary generalization with the major side effects of hyponatremia and hypersensitivity reaction[40-41].

Table 1. Conventional, new and unconventional antiepileptic drugs

Conventional	New	Unconventional
Carbamazepine (Tegretol)	Felbamate (Felbatol)	Adrenocorticotropic hormone (ACTH)
Clorazepate (Tranxene)	Gabapentin (Neurontin)	Acetazolamide (Diamox)
Clonazepam (Klonopin)	Lamotrigine (Lamictal)	Amantadine (Symmetrel)
Ethosuximide (Zarontin)	Levetiracetam (Keppra)	Bromides
Phenobarbital	Oxcarbazepine (Trileptal)	Clomiphene (Clomid)
Phenytoin (Dilantin)	Tiagabine (Gabitril)	Ethotoin (Peganone)
Primidone (Mysoline)	Topiramate (Topamax)	Mephenytoin (Mesantoin)
Valproic Acid (Depakote)	Zonisamide (Zonegram)	Mephobarbital (Mebaral)
		Methuzimide (Celontin
		Trimethadione (Tridione)

Felbamate (FELBATOL) is thought to act by the inhibition of the excitatory NMDA receptors although the exact mechanism of action remains unknown[29]. The drug is effective in the treatment of refractory partial seizure and Lennox-Gastaut syndrome since its introduction in 1993. Felbamate has been associated with multiple troublesome side effects including headache, gastrointestinal distress, weight loss, insomnia and more importantly potentially fatal aplastic anemia and liver toxicity[29]. These later side effects severely limit its use.

The new antiepileptic drugs in women, pregnancy and lactation

Some of the new AEDs particularly Gabapentin, Topiramate, Vigabatrin and Levetriacetam have minimal protein binding properties and do not cause hepatic enzyme induction, and as such do not interact with oral contraceptive pills[42]. Gabapentin and Lamotrigine have not been shown to be teratogenic in animals[43-45]. Levetriacetam is excreted in breast milk[46].

Other new antiepileptic drugs

Newer AEDs such as Pregabalin and Retigabine have been shown to be effective against partial seizures and are currently undergoing further clinical trials[46]. Fosephenytoin, a Phenytoin is useful particularly in the treatment of status epilepticus. The newer formulation of intravenous Valproate has been approved for use in patients for whom oral administration is temporarily not feasible[48].

CONCLUSION

New antiepileptic drugs are now available for the treatment of various forms of seizures and the epilepsy syndromes. Lamotrigine and Topiramate are effective as initial monotherapy for generalized seizures, and Topiramate, Lamotrigine, Oxcarbazepine and Gababentin for partial onset seizures. Zonisamide is effective as an add-on therapy for patients with partial seizures and may additionally acts as a free radical scavenger thereby provide additional protection of neurons. The difficulty encountered in treating patients with various seizure types and choosing the right AED on an individual basis particularly when new agents are being marked suggests that further research is needed in epileptogenesis, how to stop seizures, and possibly cure the underlying lesional pathology.

REFERENCES

1. Kurtzke JF, Kurland LT. The Epidemiology of Neurology. In: Joynt RJ. Clinical Neurology. Lippincott-Raven. 2002:(Vol 4);27-34.
2. Shneker BF, Fountain NB. Epilepsy. Dis Mon 2003; 49:426-78.
3. White HS. Preclinical Development of Antiepileptic Drugs: Past, Present and Future Directions. Epilepsia 2003; 44(suppl 7):2-8.
4. Stefan H, Wang Y, Pauli E, et al. A new approach in anti-epileptic drug evaluation. European Journal of Neurology 2004; 11:467-73.
5. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy. Neurology 2004; 62:1261-73.
6. National Institute for clinical Excellence-NICE guidelines. Available at:www.nice.org.uk (accessed February 2005).
7. Perucca E. Clinical Pharmacology and therapeutic use of the new antiepileptic drugs. Fundamentals & Clinical Pharmacology 2001; 15:405-17.
8. Petroff OA, Rothman DL, Behar KL, et al. The effect of gabapentin on brain gamma aminobutyric acid in patients with epilepsy. Ann Neurology 1996; 39:95-9.
9. US Gabapentin Study Group. Gabapentin as add-on therapy in refractory epilepsy. A double-blind placebo-controlled. Parallel group study. Neurology 1993; 43:2292-8.
10. UK Gabapentin Study Group. Gabapentin in partial epilepsy. Lancet 1990;335:111-7.
11. Anhut H, AshmanP, Feuerstein TJ, et al. The International Gapentin Study Group, Gabapentin (Neurontin) as add-on therapy in patients with partial seizures. A double-blind, placebo-controlled study. Epilepsia 1994; 35:795-801.

12. Genton P. When antiepileptic drugs aggravate epilepsy. Brain & Development 2000; 22: 75-80.
13. Gidal BE, Radulovic LL, Kruger S, et al. Inter and intra-subject variability in gabapentin absorption and absolute bioavailability. Epilepsy Res. 2000;40: 123-7.
14. Brodie MJ, Chadwick DW, Anhut H, et al. A double-blind comparison in newly diagnosed epilepsy. Epilepsia 2002; 43: 993-1000.
15. Cheung H, Kamp D, Haris E. An in-vitro investigation of sodium channels. Epilepsy Res 1992; 13:89-92.
16. Brodie MJ, Riches A, Yuen AW. Double-blind comparison of Lamotrigine and Carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet 1995; 345:476-9.
17. Sander JW. The Use of antiepileptic Drugs-Principles and Practice. Epilepsia 2004:45(suppl 6):28-34.
18. Patsalos PN and Peruca E. Clinically important drug interactions in epilepsy:general features and interactions between antiepileptic drugs. The Lancet Neurology; 2003;2:347-56.
19. Pellock JM. Overview of Lamotrigine and the new antiepileptic drugs: The challenge. J child Neurol 1997: 12(Supp l):48-52.
20. Schecher PJ. Clinical Pharmacology of Vigabatrin. Br. J Clin Pharmacology 1989;27: 195-227.
21. Steinhoff BJ, Hirsch E, Mutani R, et al. The ideal characteristics of antiepileptic therapy; an overview of old and new AEDs. Acta Neurol 2003: 107:87-95.
22. Chiron C, Dulac O, Beaumont D, et al. Therapeutic trial of vigabatrin on refractory infantile spasms. J child Neurol 1991:6 (Suppl 2):52-9.
23. Kraus GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction; electroretinogram and ophthalmologic findings. Neurology 1998;50:614-8.
24. Herrero AI, Del Olmo N, Gonzales-Escalada JR, et al. Two new actin topiramate: inhibition of depolarizing $GABA_A$ –mediated responses and activation of a potassium conductance. Neuropharmacology 2002;42: 220-21.
25. Russo E, Constanti A. Topiramate hyperpolarizes and modulates the slow post stimulus AHP of rat olfactory cortical neurons in vitro. Br. J. Pharmacol 2004;141:285-301.
26. Bialer M, Johannesen SI, Kupferberg HJ, et al. Progress report on new antiepileptic drugs: a summary of the Seventh Eliat conference (EILAT VII). Epilepsy Researh 2004;61:1-48.
27. Privetera M, Finchman R, Penry RE, et al. Topiramate placebo-controlled dose ranging trial in refractory partial epilepsy using 600, 00 and 1,000 mg daily dosage. Topiramate YE Study Group. Neurology 1996; 46:1684-90.
28. Faught e, Eilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose ranging trial in refractory partial epilepsy using200-, 400-, and 600 mg daily dosage:Topiramate YD Study Group. Neurology 1996;46:1684-90.
29. MacDonald RL, Greenfild J. Mechanism of actions of new anti-epilptic drugs. Curr Opinion in Neurology 1997; 10(2):121-8.

30. McKee P. Treating refractory epilepsy with tiagabine:clinical experience. Seizure 2004; 13:478-80.
31. Kellinghaus C, Dziewas R, Ludemann P. Tiagabine-related non-convulsive status epilepticus in partial epilepsy;three case reports and a review of the literature. Seizure 2002;11:243-9.
32. Janz R, Goda Y, Geppert M, et al. SV2A and SV2B function as redundant Ca2+ regulators in neurotransmitter release. Neuron 1999; 24:1003-16.
33. Lynch B, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the anti-epileptic drug Levetiracetam. Proc. Natl. Acad. Sci. 2004;101:9861-6.
34. Ben-Menachem E, Edrich P, Can Vleymen B, et al. Evidence for sustained efficacy of Levetiracetam as add-on epilepsy therapy. Epilepsy Res 2003; 53:57-64.
35. Mula M, Trimble MR, Yuen A, et al. Psychiatric adverse events during levetiracetam therapy. Neurology 2003;61:704-6.
36. Macdonald RL, Duche B. Zonisamide. Mechanism of actions in: Levy, RH, Mattson RH, Meldrum BS, Perucca E. (Eds) Antiepileptic Drugs, 5th Ed. Lippincott Williams & Wilkins, Philadelphia. 2002 : 867-72.
37. Brodie MJ, Duncan R, Vespiganni H, et al. Zonisamide is an effective adjunctive therapy for patients with refractory partial epilepsy: results from a double-blind placebo-controlled study. Epilepsia 2004: 45 (suppl 3), 155-9.
38. Lee BI, Zonisamide-adverse effects. In: Levy, R.H., Mattson RH, Meldrum BS, Perucca E (Eds). Antiepilpetic drugs 3rd Ed. Lippincott Williams & Wilkins, Philadephia. 2002 :873-9
39. Marson AG, Kadir ZA, Hutton JL, et al. The new antiepileptic drugs, a systematic review of their efficacy and tolerability . Epilepsia. 1997; 38:859-80.
40. Sabers A, Gram L. Newer anticonvulsants: Comparative Review of Drug Interaction and Adverse Effects. Drugs 2000; 60:23-33.
41. Sachedo RC, Wasserstein AG, Messenheimer JA, et al. Effects of oxcarbazepine sodium concentration and water handling. Ann Neurol. 2002; 51;613-20.
42. Karceski S, Morell M, Carpenter D. The expert consensus guideline series; treatment of epilepsy. Epilepsy Behav 2001; 2:1-50.
43. Montouris G. Gabapentin Exposure in human pregnancy: results from the Gabapentin Pregnancy Registry. Epilepsy & Behaviour 2003; 4: 310-7.
44. Tennis P, Eldridge RR, International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Preliminary results on pregnancy outcomes in women using Lamotrigine. Epilepsia 2002;43:1161-7.
45. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. Neurology 2003;61:35-42.
46. Beydoun A, Uthman BM, Kugler AR, et al. Safety and efficacy of two pregabalin regimens for add-on therapy of partial epilepsy. Neurology 2005;64:475-80.
47. Lowenstein DH. Treatment options for status epilepticus. Current Opinion in Pharmacology 2003;3:6-11.
48. Pitkanen A. New pharmacotherapy for epilepsy. Drugs. 2004 May;7(6):471-7.