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ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596
E-Mail: nmic@stjames.ie

NEW DRUGS FOR EPILEPSY

SUMMARY

- **Established antiepileptic drugs remain the mainstay of treatment. The limitations of these AEDs include lack of seizure control, side effects and drug interactions.**
- **Seizure type has the most immediate influence on choice of therapy.**
- **Newer antiepileptic drugs are generally better tolerated and are associated with fewer drug interactions.**
- **All new antiepileptic drugs are licensed for add-on therapy. Gabapentin, lamotrigine and oxcarbazepine are also licensed for monotherapy.**

INTRODUCTION

Epilepsy is the most common serious, life-threatening neurological disorder with a prevalence of 0.4-1%.[1] The majority of patients with seizures are controlled by a single antiepileptic drug (AED) but up to 30% are not well-controlled on one drug.[2,3,4,5] Established AEDs e.g. carbamazepine, phenytoin, valproate, remain the mainstay of treatment.[2] The limitations of these AEDs include lack of seizure control, side effects and drug interactions.[2,6,7,8] The impetus for the development of new AEDs has arisen from the need for more effective and better-tolerated agents.[1] Seven new drugs for epilepsy have been launched in Ireland within the past ten years namely vigabatrin, lamotrigine, gabapentin, tiagabine, topiramate, oxcarbazepine and levetiracetam.

TREATMENT

The availability of new AEDs presents the clinician with what might seem like an overwhelming choice. Usually drug therapy will be consultant led.[9] The following factors are considered when choosing one of the new AEDs:

(a) Seizure type: The diagnosis of seizure type has the most immediate influence on therapy.[3,10,11] Seizures can be subdivided into generalised (bilateral onset) such as absences, myoclonic jerks, and tonic-clonic events, or partial (focal onset) with or without secondary generalisation.[1,2,12] According to epidemiological data from Europe and the U.S, the most common type is the complex partial subtype.[12]

(b) Efficacy: There has been no systematic, well-controlled, large-scale study comparing the effectiveness of different *add-on* therapies.[3,13] A systematic review of controlled trials which included gabapentin, lamotrigine, tiagabine, topiramate and vigabatrin, suggests that topiramate and vigabatrin are more effective for partial seizures with or without secondary generalisation.[14] However, gabapentin and lamotrigine were probably not tested at their optimal doses.[15] Lamotrigine has a broad spectrum of activity against multiple seizure types and although it has been reported to cause life-threatening reactions, these occur rarely.[16] Gabapentin has favourable side effect and drug interaction profiles and would be a logical first choice adjunct therapy for refractory partial seizures, were it not for its relative lack of efficacy. *Monotherapy* trials for partial seizures demonstrated that oxcarbazepine, lamotrigine, vigabatrin and probably gabapentin have comparable efficacy and are better tolerated than carbamazepine.[17]

(c) Tolerability: Most of the common adverse effects seen with the newer agents are dose-related central nervous system (CNS) effects that appear early in treatment and often subside with time or with appropriate dosage adjustment.[6] The meta-analysis mentioned above suggests that gabapentin and lamotrigine are best tolerated. Oxcarbazepine is a useful alternative for patients who cannot tolerate carbamazepine.[14,17] Visual field defects reported with vigabatrin are a concern and careful monitoring is required.[3]

(d) Drug interactions: When adding a second drug to existing therapy the potential for an interaction must be considered.[10] The new AEDs exhibit fewer drug interactions than established AEDs.[1] Of the new AEDs, oxcarbazepine and topiramate can reduce the efficacy of the oral contraceptive pill.[2]

(e) Patient factors: These include concomitant medication, co-existing disability, and age. It is recommended that all women of child-bearing potential, with epilepsy, should take 5mg folic acid per day, irrespective of the AEDs they are taking.[27,85]

(f) Cost: See Table 2 [11,18]

Table 1: Treatment Options According to Seizure Type & Epileptic Syndrome[11]

Type of Seizure	First-line Drug	Second-line Drug
Primary generalised Absence seizure*	Sodium valproate ethosuximide	Lamotrigine
Myoclonic seizures*	Sodium valproate	Clonazepam, lamotrigine, primidone
Tonic-clonic seizures	Sodium valproate, carbamazepine, phenytoin	Lamotrigine, Phenobarbital, primidone
Absence epilepsy with onset in Childhood*	Ethosuximide	Sodium valproate, lamotrigine
Absence epilepsy with onset in Adolescence*	Sodium valproate	Ethosuximide, lamotrigine
Juvenile myoclonic epilepsy*	Sodium valproate	Clonazepam, primidone, lamotrigine
Infantile spasms (Wests Syndrome)	Vigabatrin	Clonazepam, sodium valproate
Lennox-Gastaut syndrome	Sodium valproate, lamotrigine	Carbamazepine§
Partial simple partial seizures, complex partial seizures, secondary generalized tonic-clonic seizures and partial epileptic syndromes	Carbamazepine, phenytoin	Gabapentin, lamotrigine, phenobarbital, primidone, tiagabine, topiramate, sodium valproate, oxcarbazepine, levetiracetam (add-on)

*Carbamazepine and phenytoin are contraindicated.
§Clonazepam, phenobarbital, primidone or vigabatrin may be used alternatively

(g) Monotherapy or add-on therapy?
The initial assessment of new AEDs is confined to evaluation as add-on therapy. When a drug has demonstrated efficacy in this setting it can be evaluated as monotherapy. Various factors confound the interpretation of the results from add-on trials e.g. drug interactions or synergy between the two drugs. In addition, drugs that may be beneficial in less severe forms of epilepsy may not prove effective in the refractory cases often recruited in trials.[19,20] *Monotherapy:* If the maximum tolerated dose of the first line drug fails to control seizures, another first line or a second-line drug should be added.[21] Once the second AED has been titrated to the full dose, there is an opportunity to withdraw the first AED but caution is required because of the risk of rebound seizures. Of the new AEDs only oxcarbazepine, lamotrigine and gabapentin are licensed as monotherapy agents. If monotherapy with two medications has failed, the patient should be re-evaluated.[22] Such an evaluation consists of assessing the accuracy of diagnosis of seizure type, patient compliance and consideration of a diagnosis of non-epileptic seizures. *Add-on therapy:* When monotherapy fails, the aim is to control seizures with two or at the most three AEDs.[2,13] An adequate trial of an AED is determined not by time but by the frequency of seizures i.e. the more frequent the seizures, the less time required to determine the efficacy of the drug.[11]

VIGABATRIN (Sabril®)

Overview: Vigabatrin acts by inhibiting the enzyme responsible for the breakdown of GABA (gamma aminobutyric acid) thus increasing the concentration of GABA in the brain.[23,24,25] It is indicated as add-on treatment in patients with resistant partial epilepsy with or without secondary generalisation, where all other drug combinations have proved inadequate or have not been well-tolerated.[25] Visual field defects have severely restricted its use.[26,27] It may exacerbate myoclonic or absence seizures.[3,23] Treatment may only be initiated by a specialist.[25] **Trials:** *Add-on therapy*: The major outcome trials on vigabatrin have demonstrated its efficacy in reducing seizures in >50% of patients by 44-70%.[28,29,30] One follow up study showed that 54 patients (25% of the original cohort) continued to respond at 5 yrs.[31] Another considered vigabatrin to be of marginal benefit in the long-term despite favourable results from the original trial.[86] *Monotherapy*: Three trials have compared vigabatrin with carbamazepine for monotherapy. In one trial involving 100 patients over 1 year, significantly more patients receiving carbamazepine were seizure free compared to those receiving vigabatrin. Vigabatrin was associated with fewer adverse effects. Another trial involving 51 patients over 16 weeks found that 46% of patients on vigabatrin were seizure free compared to 51% of patients on carbamazepine. Again the side-effect profile favoured vigabatrin.[32] A more recent trial (459 patients) concluded that vigabatrin was less effective but better tolerated than carbamazepine as a first-line drug for monotherapy.[24] **Dose:** The initial dose is 1g daily as add-on therapy. This may be increased by 0.5g increments weekly up to a maximum of 3g daily. Maximal efficacy is usually seen in the 2-3g daily range.[25] **Side Effects**: The most common side effects are drowsiness and fatigue.[17,23,25] Other side effects include weight gain, depression, headache, dizziness and confusion. Adverse events are usually mild and transient.[15,33] Visual field defects, which are often asymptomatic and may be irreversible, have been reported in 30 - 40% of patients. Visual field testing is necessary before treatment and at regular intervals thereafter.[15,25,26,27] **Interactions:** Vigabatrin can cause a 20–40% reduction in serum levels of phenytoin. Small decreases in phenobarbitone and primidone have also been observed.[25,32,34]

LAMOTRIGINE (Lamictal®)

Overview: Lamotrigine was first approved in Ireland in 1990 for the treatment of partial seizures and generalised seizures, including tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome. It is licensed for both monotherapy and adjunctive therapy.[35,36] Lamotrigine appears to act primarily by blocking voltage dependent sodium channels and indirectly by inhibiting glutamate release.[37,38,39] **Trials:** *Add-on therapy:* Data amassed from cross-over, placebo controlled studies has shown that when added to existing treatment, lamotrigine effected a 50% reduction in seizure frequency in 13-67% of patients and a small number became seizure free.[23,40] Lamotrigine *monotherapy* is comparable to carbamazepine for partial seizures with or without secondary generalisation and primary generalised

tonic-clonic seizures in newly-diagnosed patients.[41,42] **Dose:** For monotherapy, lamotrigine is initiated at a dose of 25mg daily for two weeks. Thereafter the dose may be titrated until optimal effect is reached or to a maximum of 500mg daily. For use as add-on therapy the dosing schedule employed is dependent on whether the patient is already taking an enzyme-inducing AED already. If the patient is already taking sodium valproate, then the titration rate should be slower. See Summary of Product Characteristics (S.P.C.) for more detailed information. **Side Effects:** Lamotrigine has been well tolerated as monotherapy. Add-on lamotrigine therapy was also well tolerated in clinical trials involving 3071 patients worldwide. The most common side effects associated with drug discontinuation were dizziness, rash, headache and nausea. In add-on trials, rash occurred in 10% of patients on lamotrigine, in 5% of patients taking placebo and lead to withdrawal of lamotrigine in 2%. Well recognised risk factors for lamotrigine-related rash include concurrent sodium valproate treatment, high starting lamotrigine dose and rapid dose escalation.[26,43,44] Most frequently, lamotrigine-induced rash is a simple morbilliform rash but more severe life-threatening forms such as Stevens Johnson Syndrome or Toxic Epidermal Necrolysis have been reported. Typically rash occurs in the first 6-8 weeks of treatment.[44,45] **Interactions:** Enzyme-inducing anticonvulsants markedly reduced serum lamotrigine concentrations, while a marked increase in serum lamotrigine is produced by valproate. Lamotrigine may increase the plasma concentration of the active metabolite (carbamazepine epoxide) of carbamazepine. Close monitoring is advisable during combination therapy with carbamazepine or oxcarbazepine.[34,36]

GABAPENTIN (Neurontin®)

Overview: Gabapentin is structurally similar to GABA, the major inhibitory neurotransmitter in the CNS. Its mechanism of action is unknown.[47,48,49] It is indicated as *add-on* therapy or *monotherapy* for patients with partial seizures with or without secondary generalisation, including patients with newly diagnosed seizures.[49] **Trials:** A recent review representing 997 patients suggests that gabapentin 1800mg daily will reduce seizure frequency by at least 50% in 28.5% of patients when used as *add-on* therapy. The trials reviewed were of short duration and provide no evidence for long term efficacy.[50] Three large, double-blind trials have provided good evidence of the safety and efficacy of gabapentin as *monotherapy* for the treatment of partial onset seizures.[51] **Dose:** The usual starting dose is 300mg on day 1 then 300mg twice daily on day 2, then 300mg three times daily on day 3. Thereafter the dose can be increased in increments of 300mg daily (in 3 divided doses) up to a maximum of 3600mg daily. The usual dose is 900 -1200mg daily. A reduction in dosage may be necessary in the elderly and in renally compromised patients.[27,49] **Side Effects:** Gabapentin has been evaluated for safety in more than 2000 patients. It is well-tolerated. Drowsiness, dizziness, ataxia headache and fatigue are the most common adverse effects. Most adverse reactions subside upon dosage reduction.[27,48,49,52,53] **Interactions:** Gabapentin has been shown to have no effect on the serum concentration of the combined oral contraceptive pill. An isolated report describes increased phenytoin levels and toxicity in one patient when given gabapentin.[34,49,53]

TIAGABINE (Gabitril®)

Overview: Tiagabine is the first GABA uptake inhibitor to be introduced into clinical practice. It increases brain levels of GABA.[19,23,54] It is licensed as add-on treatment for partial seizures with or without secondary generalisation.[55] **Trials:** Five double-blind, placebo-controlled trials have evaluated the efficacy of tiagabine as add-on treatment in a total of 951 patients with refractory partial seizures with or without secondary generalisation. An analysis of all five studies demonstrated that tiagabine was superior to placebo in preventing simple partial seizures (30 vs. 10%), complex partial seizures (27 vs. 13%) and secondary generalised seizures (40 vs. 30%). The measure chosen for efficacy was the number of patients with a ≥50% reduction in seizure frequency. Tolerance did not occur with long-term treatment (up to 12mths or more)[19,54,56-58] When used as *monotherapy,* tiagabine has been beneficial in some patients but the results of ongoing studies are awaited.[19,58] **Dose:** The initial dose is 7.5-15mg daily followed by weekly increments in steps of 5-15mg daily. As adjunctive therapy in patients taking enzyme-inducing drugs e.g. carbamazepine, the usual maintenance dosage is 30-50mg daily; doses up to 70mg daily are well tolerated. In patients not taking enzyme-inducing drugs, the maintenance dose is 15-30mg daily. Dosage should be reduced in hepatic impairment.[23,27,55,59] **Side Effects:** Most adverse effects are mild to moderate in intensity and transient in nature. Dizziness, asthenia, nervousness, tremor, diarrhoea and depressed mood were reported more frequently with tiagabine than with placebo in clinical trials.[23,58] **Interactions:** Tiagabine metabolism is accelerated by antiepileptics that are enzyme-inducers e.g. carbamazepine, phenytoin, phenobarbitone, primidone. Plasma concentrations of tiagabine may be reduced by threefold.[23,59]

TOPIRAMATE (Topamax®)

Overview: Topiramate is a novel antiepileptic agent with multiple mechanisms of action including blockade of sodium channels, GABA potentiation and antagonism of the excitatory activity of one type of glutamate receptor.[60-62] It is indicated as adjunctive therapy for the treatment of partial seizures and primary generalised tonic-clonic seizures.[60] **Trials:** Six multicentre, double-blind, placebo-controlled studies have demonstrated the efficacy of topiramate as adjunctive therapy for refractory partial onset seizures with or without secondary generalisation. The incidence of seizures was decreased by > 50% in 43% of patients. Subsequent studies have confirmed these results. In addition, topiramate has been shown to be effective as adjunctive therapy for generalised tonic-clonic seizures.[17,63-65] The therapeutic effect and tolerability were maintained with long-term therapy (up to 7yrs).[61,66,67] Although not licensed for monotherapy, studies have also shown that topiramate monotherapy is effective in some patients with partial epilepsy.[17,68] **Dose:** Therapy should be initiated at a dose of 50mg at night for one week and increased by 50 to 100mg at weekly intervals according to response. The minimal effective dose is 200mg daily. The maximum dose is 1600mg daily. Most patients are maintained on 200 – 400mg daily in two divided doses.[23,60] **Side effects**: Most adverse effects reported were mild to moderate in severity and lessen with continued treatment.[61,68,69] Slow dose escalation reduces the incidence. CNS effects are the most common (headache, impaired concentration, somnolence, fatigue, dizziness). Paraesthesia, weight loss and the development of renal stones have also been reported. Adequate hydration is recommended to prevent the latter.[23,61,66,68,70] **Interactions:** Phenytoin and carbamazepine can decrease the plasma concentration of topiramate by about 50% hence a dosage adjustment may be necessary.[23,60] The efficacy of low dose e.g. 20mcg ethinyloestradiol-containing oral contraceptives may be reduced by topiramate. If a combination oral contraceptive pill is required, one containing >35mcg of ethinyloestradiol should be prescribed.[61,68] In the occasional patient, topiramate may increase the plasma concentration of phenytoin.[64] In one study the serum digoxin level was decreased when taken with topiramate.[60,64]

OXCARBAZEPINE (Trileptal®)

Overview: Oxcarbazepine, a derivative of carbamazepine has recently been licensed for the treatment of partial seizures, with or without secondary generalised seizures. It is indicated for use as *monotherapy* as well as *adjunctive therapy*.[23,71] Its mechanism of action is similar to that of carbamazepine, however, patients on carbamazepine have received additional benefit when oxcarbazepine was added, possibly indicating another mechanism of action.[71-73] **Trials:** A recent review of two trials (961 patients) concluded that oxcarbazepine was effective as an *add-on treatment* for drug-resistant partial epilepsy in the short term (4-6 mths).[50] Results of another study (692 patients) in a similar patient cohort showed that oxcarbazepine was significantly more effective than placebo (over 28 weeks).[73] *Monotherapy* trials have demonstrated comparable efficacy to the standard anticonvulsant drugs and better tolerability compared to phenytoin and carbamazepine.[46,74,75] **Dose:** For *monotherapy* the initial dose is 600mg daily, given in 2 divided doses. This dose can be increased by a maximum increment of 600mg daily at approximately weekly intervals up to 2400mg daily. For *add-on therapy* the same dosing guidelines apply. Renal impairment necessitates halving the initial dose to 300mg daily and increasing, if necessary, under careful observation.[71] **Side Effects:** The most common side effects are dizziness, somnolence, headache, fatigue, nausea and vomiting.[71,75] Hyponatraemia can occur and monitoring is advisable in the elderly, in patients with renal conditions associated with low sodium and those on NSAIDs or diuretics.[46,71,76] Caution is necessary in heart failure (monitor body weight) and cardiac conduction disorders.[27] **Interactions**: Oxcarbazepine produces minimal hepatic enzyme induction but like carbamazepine and the older anti-epileptic drugs, appears to decrease the effectiveness of oral contraceptives.[72] It can decrease the serum level of calcium antagonists and of carbamazepine. It can raise phenytoin and phenobarbitone levels. Plasma levels of an active metabolite of oxcarbazepine can be decreased by carbamazepine, phenytoin, phenobarbitone or valproic acid.[27,71]

LEVETIRACETAM (Keppra®)

Overview: Levetiracetam is chemically unrelated to existing anti-epileptic drugs. It is indicated as adjunctive therapy for partial seizures with or without secondary generalisation.[71,77] Its mechanism of action is unknown. **Trials:** The anticonvulsant efficacy of levetiracetam as add-on therapy in the treatment of refractory partial seizures (simple and/or complex) with or without secondary generalisation has been assessed predominantly in three double-blind, randomised, placebo-controlled, multicentre trials (904 patients). Levetiracetam 1000mg, 2000mg and 3000mg daily for up to 18 weeks significantly reduced the frequency of partial seizures when administered with other anticonvulsant drugs, the percentage reduction over placebo was 16.4 %, 17.7% and 27.7% respectively.[78-81] The efficacy of adjunctive levetiracetam was maintained during long-term treatment, (2 years).[1] One small trial (86 patients) demonstrated the efficacy of levetiracetam 3000mg daily as monotherapy in patients with refractory partial seizures. This is not, as yet, an approved indication.[81] **Dose:** The initial adult dose is 1000mg daily. This dose can be increased, depending on clinical response and tolerance, up to a maximum of 3000mg daily. Treatment should be administered in two divided doses.[1,77] **Side Effects:** Levetiracetam was generally well-tolerated in clinical trials. The main side effects observed were somnolence, asthenia, headache and dizziness.[1,78,82] **Interactions:** Levetiracetam has a low potential for drug interactions. No pharmacokinetic interaction was observed with other anticonvulsant agents (phenytoin, carbamazepine, valproic acid, phenobarbitone, lamotrigine, gabapentin and primidone), oral contraceptives (ethinyloestradiol and levonorgestrel), digoxin or warfarin.[1,77,82,83]

CONCLUSION

The ultimate aim of epilepsy treatment is to eliminate seizures using drugs with minimal adverse effects.[84] Although the new AEDs are welcome adjuncts or alternatives to existing therapy, more experience with their use is needed before their place in therapy is fully established.

TABLE 2: Cost of Antiepileptic Drugs (Based on GMS Prices –May 2001)

Drug	Daily Dosage Range	Cost (£)
Vigabatrin	1g-3g	0.98-2.96
Lamotrigine	25mg-500mg	0.42-5.64
Gabapentin	300mg-3600mg	0.54-5.56
Tiagabine	7.5mg-70mg	1.00-6.72
Topiramate	50mg-400mg	0.67-4.51
Oxcarbazepine	600mg-2400mg	0.68-2.71
Levetiracetam	1g-3g	2.13-6.21

References available on request.