Epileptic Disord 2003; 5 (Suppl 1): S65–S72

Role of levetiracetam in the treatment of epilepsy

Martin J. Brodie[1], Jacqueline A. French[2]

[1] Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow, Scotland, United Kingdom
[2] Penn Epilepsy Centre, Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

ABSTRACT – Physicians treating patients with epilepsy have a host of therapeutic options. Drug choice is dictated first by the seizure(s) and/or epilepsy syndrome. Age is also a factor. Special considerations apply to women, particularly during their childbearing years, and to patients who are learning-disabled. Drug selection is further influenced by such characteristics as spectrum of activity, rapid response, low potential for drug-drug interactions, and ease of use. In addition to clinical trial data, postmarketing assessments of the new antiepileptic drugs provide useful clinical information on efficacy and safety. Levetiracetam has specific characteristics that make it an optimal choice for many patient populations.

KEY WORDS: antiepileptic drugs, epilepsy, levetiracetam, seizures

Introduction

The majority of people with newly diagnosed epilepsy in the developed world receive prophylactic antiepileptic drug (AED) therapy with the aim of keeping them free of seizures. Successful control can be achieved in 60% to 70% of patients [1, 2]. Many will respond to a moderate dose of the first AED [3]. Indeed, lack of response to the initial treatment is a powerful predictive factor for subsequent refractoriness [1, 4]. Other prognostic indicators in teenagers and adults with partial and generalized tonic-clonic seizures include a large number of pretreatment seizures [1, 5] and the presence of an underlying structural abnormality, such as mesial temporal sclerosis or cortical dysplasia [6, 7]. There is now increasing evidence that patients at risk for refractory epilepsy can be identified early and targeted for effective therapeutic intervention [8]. Epilepsy is a progressive disorder in some patients and so an aggressive approach early in the course of the disease may prevent subsequent refractoriness [9].

Antiepileptic drugs

Nine new AEDs have been licensed over the last decade, giving many more therapeutic options to the patient and his or her doctor [10]. Levetiracetam was the last of these to be launched at the end of the 20th century. Positive and negative features of the other eight newer AEDs are summarized in *table 1* [11]. Some of the most important factors that support the clinical value of a successful AED are broad spectrum of activity, ease of use, lack of pharmacokinetic interactions, and rapid response to initiation of therapy. There is, in addition, emerging evidence in support of combining drugs with different and possibly complementary mechanisms of action [12,13]. Summaries of the currently known mechanisms of action and efficacy against common seizure types for a range of established and modern AEDs are given in *tables 2 and 3* [10, 14].

Correspondence:
Martin J. Brodie
Epilepsy Unit, Western Infirmary
Glasgow G11 6NT
Scotland, United Kingdom
Phone: + (44) 141 211 2572/2944
Fax: + (44) 141 334 9329
E-mail: Martin.J.Brodie@clinmed.gla.ac.uk

Table 1. Perceived advantages and disadvantages of modern antiepileptic drugs

Drug	Advantages	Disadvantages
Gabapentin	Well tolerated	Variable absorption
	No idiosyncratic reactions	Thrice-daily administration
	No interactions	Weight gain
Lamotrigine	Predictable kinetics	Dose-related rash
	Wide spectrum of activity	Slow titration
	Non-sedative	Interaction with carbamazepine
Oxcarbazepine	Predictable kinetics	Occasional rash
	Defined spectrum of activity	Interaction with oral contraceptives
	Good neuropsychiatric profile	Hyponatraemia
Topiramate	Powerful efficacy	Slow titration schedule
	Wide spectrum of activity	Word-finding difficulties
	No idiosyncratic reactions	Renal stones
Tiagabine	Specific mode of action	Dizziness
	No idiosyncratic reactions	Inducible metabolism
	Target only interactions	Thrice-daily administration
Zonisamide	Long half-life	Sedative
	Wide spectrum of activity	Neurotoxicity
	Few interactions	Renal stones
Felbamate	Wide spectrum of activity	Pharmacokinetic interactions
	Non-sedative	Interaction with oral contraceptives
	Powerful efficacy	Aplastic anaemia/hepatotoxicity
Vigabatrin	Easy to use	Initial sedation
	No idiosyncratic reactions	Psychiatric side-effects
	Few interactions	Concentric visual field defects

Special populations

When selecting an AED, the first priority should be to choose a drug that is appropriate for the patient's seizure(s) and/or epilepsy syndrome. However, for most patients, this will leave a large number of potential drug choices. A population-based strategy can further refine the choice of the most appropriate AED for a particular patient. Different subpopulations within the epilepsy community have special needs, which can be best served by AEDs with certain characteristics. Specific populations may be defined by age, gender, or situation (e.g., first add-on, refractory). Some of these populations, and the issues that must be considered before making treatment decisions, are discussed below.

Teenagers

Epilepsy commonly becomes manifest during adolescence, particularly peri-puberty. Partial epilepsies may initially present in childhood, followed by a seizure-free interval and re-emergence in adolescence [15]. Idiopathic generalized epilepsies often begin in adolescence. One idiopathic syndrome, juvenile myoclonic epilepsy, almost always begins in adolescence or young adulthood. Juvenile myoclonic epilepsy is usually diagnosed after the occurrence of generalized tonic-clonic convulsions (GTCC). The EEG may demonstrate a 3 to 5 hz generalized spike-wave, often associated with polyspikes, or may be normal. If an adolescent presents with GTCC, it is important to ask specifically whether myoclonus is occurring, as it is rarely spontaneously reported by the patient and may be the key to a correct diagnosis. Juvenile myoclonic epilepsy is an important syndrome to recognize and diagnose, since it does not respond to narrow-spectrum drugs *(table 3)*.

The emergence of epilepsy at this critical developmental stage is particularly problematic, for several reasons. Because teenagers may have issues with independence and

Table 2. Common mechanisms of action for a range of antiepileptic drugs

Drug	Na^+ channels	Ca^+ channels	K^+ channels	Inhibitory transmission	Excitatory transmission
Phenytoin	+ + +	+			
Carbamazepine	+ + +				
Sodium valproate	+	+		+ +	+
Ethosuximide		+ + +			
Phenobarbital		+		+ + +	+
Benzodiazepines				+ + +	
Gabapentin	+	+		+ +	
Lamotrigine	+ + +	+			
Oxcarbazepine	+ + +	+	+		
Topiramate	+ +	+ +		+ +	+ +
Tiagabine				+ + +	
Zonisamide	+ +	+ +			
Levetiracetam		+	+	+	+
Felbamate	+ +	+		+ +	+ +
Vigabatrin				+ + +	

Key: + + + = primary action; + + = probable action; + = possible action.

separation from authority figures, compliance with treatment may be a problem. Drugs selected for this population should have a simple regimen that is easy to adhere to. School performance at this juncture is likely to have an enduring impact on future achievement and opportunities. It is, therefore, best to select an AED that is not sedating and does not impair concentration or cognitive ability. Since adolescence is a time when good self-image and self-esteem are critical, drugs that produce cosmetic changes such as hirsutism, gum hypertrophy, and weight increase should be avoided. Finally, adolescence may be associated with issues of emerging sexuality, and so contraception may be a concern. Patients with established epilepsy should be scheduled for a follow-up visit when they reach adolescence, to discuss the impact of drug and alcohol use, non-compliance, and sleep deprivation on epilepsy.

Levetiracetam has several characteristics that may make it a good choice in adolescence. It is a broad-spectrum agent. Several open-label studies have suggested that it is effective in juvenile myoclonic epilepsy, and further controlled studies are ongoing [16, 17]. There are no known

Table 3. Efficacy against common seizure types for a range of antiepileptic drugs

Drug	Partial	Tonic-clonic	Absence	Myoclonic	Atonic/tonic
Phenytoin	+	+	—	—	—
Carbamazepine	+	+	—	—	—
Sodium valproate	+	+	+	+	+
Ethosuximide	0	0	+	0	0
Phenobarbital	+	+	—	? +	—
Benzodiazepines	+	+	?	+	+
Gabapentin	+	+	—	—	0
Lamotrigine	+	+	+	? +	+
Oxcarbazepine	+	+	—	—	—
Topiramate	+	+	?	+	+
Tiagabine	+	+	—	—	0
Zonisamide	+	+	? +	+	? +
Levetiracetam	+	+	+	+	?
Felbamate	+	+	? +	? +	+
Vigabatrin	+	+	—	—	?

Key: + = efficacy; ? + = probable efficacy; **0** = ineffective; – = worsens seizures; ? = unknown.

cosmetic side effects, and levetiracetam is weight-neutral. Cognitive complaints are not common. In addition, levetiracetam can be taken in a simple, twice-a-day regimen and has no effect on the hormonal components of oral contraceptives.

Women of childbearing age

There are special considerations when AEDs, either established or modern, are given to women, particularly during their childbearing years. Choice of therapy may be influenced by the potential impact of treatment on hormonal function, sexuality, and pregnancy. Physicians treating women with epilepsy must be aware of these issues in order to provide optimal care.

Many AEDs are hepatically metabolized and some of these alter the metabolism of other drugs, hormones, and vitamins [18]. The most potent inducers of hepatic enzymes are phenytoin, carbamazepine, and the barbiturates. Oxcarbazepine, topiramate, and felbamate selectively induce hepatic metabolism. Sodium valproate, on the other hand, inhibits hepatic metabolism. The inducing/
inhibiting effects of these drugs are particularly important when treating women, because the hormonal milieu may be affected, leading to alteration in the menstrual cycle and ovulation [19]. The induction of vitamin D metabolism may lead to increased risk of osteomalacia and osteoporosis. Vitamin D and calcium supplementation is advisable in all young women but is particularly important when enzyme-inducing AEDs are prescribed. These effects are undergoing intense study [20]. The estrogen and progesterone component of oral contraceptives and the components of depo-forms of steroid hormones are also hepatically metabolized and should at best be avoided by women on enzyme-inducing AEDs. The impact of enzyme induction/inhibition on women in their childbearing years is not completely known, but if non-inducing agents are an option, they may be preferable in this population.

Women should be counselled about the potential teratogenicity of AEDs. More is known about the risks of established drugs than new and emerging drugs. Essentially, all of the established drugs may cause a similar group of minor anomalies known collectively as the fetal anticonvulsant syndrome [21]. These include craniofacial and digital anomalies. Of more concern is the 1% to 6% incidence of major anomalies, including cardiac defects, cleft lip and palate, microcephaly, and developmental delay. Neural tube defects can be caused by carbamazepine (0.5% risk) and sodium valproate (1% risk). Risks are increased when polytherapy or high doses are used. No specific anomalies have been associated with the newer AEDs, but there is not enough evidence to determine that they are safe. Ongoing data collection through prospective pregnancy registries will provide much-needed data. In the meantime, precautions can be taken to ensure the safest possible pregnancy. These include avoiding polytherapy where possible, using the lowest effective dosages, and prescribing at least 1 mg of folate for all women of childbearing age, regardless of whether they express a desire to become pregnant in the immediate future [19].

Levetiracetam has no impact on hepatic metabolism through the cytochrome P 450 system [22]. Therefore, it has no known effect on the hormonal milieu or bone metabolism. Levetiracetam does not interact with oral contraceptives [23] nor, presumably, with depo-forms of contraception [24].

Elderly people

Old age is now the most common time of life for epilepsy to develop [25]. Most elderly patients have partial seizures with or without secondary generalization, often as a consequence of cerebrovascular disease, dementia, tumor or trauma, although not always [26]. The pharmacokinetics of AEDs differ in the elderly because of altered volume of distribution, lower protein binding, impaired hepatic metabolism, reduced enzyme inducibility, and slower renal elimination. Heightened receptor sensitivity and impaired homeostatic mechanisms result in greater susceptibility to side effects, especially neurotoxic effects. Idiosyncratic reactions are also more common in older people. The ideal drug for the elderly would be one that is fully absorbed and has linear pharmacokinetics, with clearance unaffected by renal impairment. Such an ideal AED would not induce or inhibit hepatic mono-oxygenase or conjugating enzymes, interact with concomitant medication, or produce neurotoxic or other side effects. An established target dose could be achieved without titration. Formulations would be readily identifiable, palatable, and easily swallowed. Levetiracetam fulfils the majority of these requirements and may prove to be a valuable therapeutic option in this patient population.

Learning disability

The prevalence of epilepsy in people with learning disability ranges from 5% in mildly affected individuals to 75% if there is co-existent severe cerebral palsy or brain injury [27]. Individuals with developmental delay are a unique population, for several reasons. Often their cognitive disturbance results from a diffuse brain insult or disorder, which also leads to frequent and difficult-to-treat seizures. For example, patients with the Lennox-Gastaut syndrome present with the triad of mental retardation, a pathognomonic EEG disturbance (slow spike-wave), and difficult-to-control seizures with multiple seizure types. Seizures in these patients have both partial and generalized characteristics. Therefore, broad-spectrum agents such as sodium valproate, lamotrigine, zonisamide, topiramate, and levetiracetam are of greatest use. Although tonic-clonic seizures are common, some patients also have partial events, atypical absences, myoclonic jerks,

and drop attacks. The clinical picture may be confused by stereotypic movements and behavioural disorders that can be mistaken for seizures. Electrophysiological investigation and brain imaging, if available, are often unhelpful. Diagnosis depends on an accurate description of events by a witness or, ideally, a home video of the episodes if the diagnosis is in doubt. Sometimes inpatient video-EEG monitoring is useful to distinguish seizures from other events.

Seizure freedom is a realistic, though not always attainable, goal for many learning-disabled people with epilepsy. An individualized management plan should be devised for each patient, allowing numbers and doses of AEDs to be rationalized. Attention should be paid not just to seizure severity and frequency, but also to other lifestyle factors such as mood, appetite, sleep, behaviour, cooperation, and communication. Many but not all patients with developmental delay will require polytherapy to achieve optimal seizure control. For this patient group, as with other groups, complete seizure control may not be the goal if it is at the expense of alertness, cognition, or quality of life. Elimination of dangerous and disabling seizures may be the most important end point. When new drugs are added, it is important to closely monitor the patient for side effects such as cognitive slowing and lethargy. In this population, as doses are raised or drugs are added, there may be a subtle build-up of negative cognitive effects, which can eventually have a profound impact on quality of life.

Often, patients with developmental delay are first seen when they have been treated for many years and are already on a polytherapy regimen. It is often beneficial to try to simplify the regimen and eliminate drugs with the greatest negative cognitive impact, such as benzodiazepines and barbiturates. However, all changes should be made very gradually and with extreme care, as these patients have a high potential for seizure exacerbation and even status epilepticus when their medications are changed. Side-effect profiles of AEDs may differ in the developmentally delayed. In particular, some AEDs appear to cause aggression in some patients, while improving alertness in others. These include levetiracetam, lamotrigine, and felbamate. If the patient experiences significant improvement in seizure control, antipsychotic agents may be effective in treating this side effect.

Our early experience with levetiracetam in this patient population is encouraging and will be discussed in more detail later in this paper.

First add-on

When patients do not become seizure-free on their first or second AED, there are several strategies for continued treatment [8]. One possible option is to convert the patient to another monotherapy. However, removing a drug may involve risk of worsening, so physicians and patients sometimes opt to add a second drug. The concept of polytherapy was frowned upon in the past, but with the advent of new drugs with novel mechanisms and fewer drug interactions, "rational polytherapy" is becoming more appealing [12]. This is where the more modern agents are at a substantial advantage compared with older drugs.

Several specific characteristics make a drug a good choice as the initial add-on agent. A novel mode of action theoretically provides optimal potential for additive benefit. Many of the new drugs have novel mechanisms, some of which have not been completely elucidated [14]. Another important characteristic is the presence or absence of drug-drug interactions. Equally important as pharmacokinetic interactions is the potential for pharmacodynamic interactions, which occur when coadministration causes more than additive toxicity or benefit without changing serum concentrations. These interactions may occur because of similarities in the side-effect profiles of the coadministered drugs. This is the likely explanation behind the adverse pharmacodynamic interactions between lamotrigine and carbamazepine, and carbamazepine and phenytoin. These drug combinations, although in some cases beneficial, should not be used as first choice.

Table 4 shows common central nervous system side effects which occurred in randomized placebo-controlled add-on studies of the new drugs. Levetiracetam has a relatively low incidence of fatigue and dizziness in this add-on situation. There are no pharmacokinetic interactions. Also, its mechanism of action appears unique and differs from other marketed drugs (see the article by Drs. Klitgaard and Pitkänen in this supplement).

Refractory epilepsy

When standard AEDs fail to control seizures, the patient's epilepsy is by definition treatment-resistant, or refractory [9]. The impact of new AEDs on such patients has been well studied in placebo-controlled add-on trials. Once many drugs have failed, the primary concern is to find a highly efficacious drug or combination. At this point, although side effects, drug interaction profiles, and frequency of dosing are important considerations, they may take a back seat to the goal of seizure freedom. Unfortunately, none of the newer AEDs have produced a high percentage of seizure-free patients in controlled trials in refractory epilepsy. Often, seizure-free rates are not even provided in such reports. Responder rates (50% or greater reduction in seizure frequency) are routinely given. Drugs for refractory epilepsy must also be demonstrated to have efficacy that persists over the long term.

Levetiracetam has been demonstrated to be useful add-on therapy in refractory patients. In add-on studies in this population, responder rates range from 23% to 33% at a dose of 1000 mg/day and to 42% at a dose of 3000 mg/day, compared with 10% to 17% for patients on

Table 4. Common central nervous system side effects reported for the new antiepileptic drugs (AEDs) with placebo rates subtracted (percent of patients reporting problems) [33-41]

Side effect	GBP (543/378)*	LTG (711/419)*	TGB (494/275)*	OXC (171/139)*†	TPM (113/174)*‡	LEV (769/439)*	ZNS (269/230)*
Dizziness	10	25	12	19	14	5	6
Ataxia	7	16	2	12	14	2	5
Speech/language	—	—	—	1	19	—	3
Diplopia	4	21	—	25	8	1	—
Headache	—	10	—	5	—	1	2
Paresthesia	—	—	—	0	12	1	3
Tremor	4	—	6	3	5	—	—
Incoordination	—	4	—	2	3	2	5
Blurred vision	—	11	—	10	—	—	—

*AED/placebo; † 1200 mg dose information used; ‡ 200-400 mg dose information used; **GBP** = gabapentin; **LTG** = lamotrigine; **TGB** = tiagabine; **OXC** = oxcarbazepine; **TPM** = topiramate; **LEV** = levetiracetam; **ZNS** = zonisamide.

placebo. Up to 8% of patients were seizure-free when dosed with 3000 mg/day [28-30]. This compares favourably with other new therapies [31].

Personal experience

Glasgow study

A prospective observational study in patients with difficult-to-control epilepsy is under way at the Epilepsy Unit in Glasgow. At least 150 patients will be recruited, including a cohort with learning disabilities. Patients will be followed until they reach an end point in the study. The major aim of the project is to establish the efficacy, tolerability, and dosing of adjunctive levetiracetam in clinical practice. Efficacy end points include seizure freedom for at least 6 months and seizure reduction 50% or greater for 6 months (responder) at optimum levetiracetam dosage compared with a 3-month prospective baseline. Patients with any seizure type or epilepsy syndrome can be included in the study. The starting levetiracetam dose is 500 mg twice daily, which can be reduced if sedation becomes a problem. Learning-disabled patients are started on a lower amount. Dosage is titrated until seizure freedom is attained or to the limit of tolerability. Concomitant medication can be discontinued. Preliminary results are summarized in *table 5*.

This study will assess the efficacy of levetiracetam across a range of seizure types. Although a cohort of patients did report sedation, some resulting in withdrawal from the study, others felt calmer and more in control of their lives. These positive psychotropic effects merit further investigation. No rashes or other idiosyncratic reactions have occurred in any patient receiving treatment with levetiracetam. Some patients withdrew from the study due to lack of efficacy. Other reasons for discontinuing levetiracetam included headache, weight gain, and hallucinations. Limited histories of four illustrative cases follow.

Case 1: 56-year-old male

This man developed partial seizures and secondary generalization with frontal lobe semiology in 1959 at age 13. Complete seizure control had never been achieved despite treatment with therapeutic regimens involving phenytoin, carbamazepine, and vigabatrin. The basis for his epilepsy is unclear. Surface EEG has repeatedly shown left hemispheric dysfunction and occasional left frontal epileptic discharges. Brain imaging was normal. There was no history of birth trauma or febrile convulsions. A maternal uncle had generalized tonic-clonic seizures. In March 1994, the patient entered a double-blind, placebo-controlled trial of levetiracetam. He had 12 documented complex partial/secondary generalized seizures per month during baseline while receiving treatment with carbamazepine retard 600 mg twice daily (plasma level 40.1 µmol/L). Within a few days of starting the study, he became seizure-free. This situation continued when he was transferred to open-label levetiracetam at a dose of 1000 mg twice daily. He has been free of seizures for more than 8 years on the combination of controlled-release carbamazepine and levetiracetam.

Table 5. Preliminary outcome data with levetiracetam in Glasgow study

Outcome	Normal population	Learning-disabled	Total
Seizure-free	22	11	33
Responders*	15	6	21
Marginal effect†	9	1	10
Discontinued	30	10	40
Ongoing	43	15	58
Total	119	43	162

*Responder ≥ 50% seizure reduction. †Marginal effect < 50% seizure reduction.

Case 2: 26-year-old male

This man developed myoclonic jerking with occasional tonic-clonic seizures at age 16. Routine EEG showed features consistent with juvenile myoclonic epilepsy. Brain imaging was normal. There was no history of birth injury or febrile convulsions during childhood or a family history of epilepsy. Initial treatment with carbamazepine in a non-specialist setting exacerbated the problem. He was referred to the Epilepsy Unit in Glasgow on sodium valproate (1200 mg twice daily). Despite this, he continued to report weekly myoclonic jerks and nocturnal tonic-clonic seizures. The valproate dose was increased to 1500 mg twice daily with consistent concentrations around 600 µmol/L, indicating good compliance. No improvement in seizure control was achieved. The addition of lamotrigine was not tolerated due to worsening tremor. Since levetiracetam (500 mg twice daily) was added to the valproate on 29 March 2001, the patient has been seizure-free.

Case 3: 68-year-old female

This woman has had partial seizures with secondary generalization since 1956. She had received treatment with phenobarbital, phenytoin, sodium valproate, gabapentin, and topiramate. When referred to the Epilepsy Unit in Glasgow she was documenting many simple/complex partial seizures daily despite phenytoin 300 mg daily (plasma level 76 µmol/L). Magnetic resonance imaging (MRI), undertaken in January 2000, revealed diffuse atrophy of the left hippocampus. Levetiracetam 1000 mg twice daily was added by increments to the phenytoin, and she has been seizure-free since April 2000. She reports feeling calmer and more competent.

Case 4: 39-year-old male

This man has been mildly learning-disabled since birth. He developed absence and myoclonic and tonic-clonic seizures at the age of 3. There was no family history of epilepsy or birth trauma. After some years he developed falling episodes accompanied by shaking of the left leg and arm lasting about 1 min. Routine EEG showed disorganized activity with runs of paroxysmal epileptiform discharges and evidence of a right fronto-temporal focus. Ambulatory EEG recorded nine attacks in 48 hours. MRI of brain was normal. The patient demonstrated intermittent episodes of aggression. The clinical picture was one of idiopathic generalized and localization-related epilepsies. Over the years, the patient was treated with phenytoin, carbamazepine, sodium valproate, clonazepam, clobazam, lamotrigine, tiagabine, and topiramate in different combinations. In May 1998, treatment was initiated with levetiracetam in addition to the existing schedule of carbamazepine retard and sodium valproate chrono. At that time, his family was reporting clusters of secondary and possibly primary generalized tonic-clonic seizures every 10 days followed by 2 to 3 days of absences and myoclonic jerks. He became seizure-free in July 1998 on carbamazepine retard 600 mg am/800 mg pm, sodium valproate 1.5 g am/2 g pm, and levetiracetam 1.5 g am/2 g pm daily. He has had occasional tonic-clonic seizures during intercurrent infections only. Over the past few years his behaviour and self-confidence have improved.

Conclusion

Levetiracetam can be introduced as first-choice add-on treatment for patients with localization-related or idiopathic generalized seizures. Most will tolerate an initial dose of 500 mg twice daily without complaint, with further weekly increments in dosage up to 2000 mg or 3000 mg daily as necessary. A few patients will need and tolerate higher amounts. Many will achieve complete seizure control on smaller doses. If sedation is reported on initiation, slower dosage titration is recommended. Tolerability may be a limiting factor in some of these patients. Apart from sedation, behavioural changes have been noted in a few patients [32]. These results of levetiracetam in clinical practice support its potential as an important addition to the therapeutic armamentarium for the management of epilepsy.

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; 342: 314-9.

2. Berg AT, Shinnar S, Levy SR, *et al*. Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. *Epilepsia* 2001; 42: 1553-62.

3. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; 42: 1255-60.

4. Dlugos DJ, Samuel MD, Strom BL, *et al*. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. *Neurology* 2001; 57: 2259-64.

5. MacDonald BK, Johnson AL, Goodridge DM, *et al*. Factors predicting prognosis of epilepsy after presentation with seizures. *Ann Neurol* 2000; 48: 833-41.

6. Semah F, Picot MC, Adam C, *et al*. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998; 51: 1256-62.

7. Stephen LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001; 42: 357-62.

8. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology* 2002; 58(Suppl 5): S2-8.

9. Arroyo S, Brodie MJ, Avanzini G, *et al*. Is refractory epilepsy preventable? *Epilepsia* 2002; 43: 437-44.

10. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. *Lancet* 2000; 356: 323-9.

11. Brodie MJ, Kwan P. The star systems: overview and use in determining antiepileptic drug choice. *CNS Drugs* 2001; 15: 1-12.

12. Deckers CL, Czuczwar SJ, Hekstar YA, *et al*. Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. *Epilepsia* 2000; 41: 1364-74.

13. Stephen L, Brodie M. Seizure-freedom with more than one antiepileptic drug. *Seizure* 2002; 11: 349-51.

14. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacol Ther* 2001; 90: 21-34.

15. French JA, Williamson PD, Thadani VM, *et al*. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 1993; 34: 774-80.

16. French J. Use of levetiracetam in special populations. *Epilepsia* 2001; 42(Suppl 4): 40-3.

17. Greenhill L, Betts T, Smith K. Effect of levetiracetam on resistant juvenile myoclonic epilepsy. *Epilepsia* 2001; 42(Suppl 7): 179.

18. Patsalos PN, Froscher W, Pisani F, *et al*. The importance of drug interactions in epilepsy therapy. *Epilepsia* 2002; 43: 365-85.

19. Zahn CA, Morrell MJ, Collins SD, *et al*. Management issues for women with epilepsy: a review of the literature. *Neurology* 1998; 51: 949-56.

20. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: epidemiology, mechanisms and therapeutic implications. *CNS Drugs* 2001; 15: 633-42.

21. Moore SJ, Turnpenny P, Quinn A, *et al*. A clinical study of 57 children with fetal anticonvulsant syndromes. *J Med Genet* 2000; 37: 489-97.

22. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* 2000; 85: 77-85.

23. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. *Epilepsia* 2002; 43: 697-702.

24. Benedetti MS. Enzyme induction and inhibition by new antiepileptic drugs: a review of human studies. *Fundam Clin Pharmacol* 2000. 14: 301-19.

25. Hauser WA. Seizure disorders: the changes with age. *Epilepsia* 1992; 33(Suppl 4): S6-14.

26. Stephen LJ, Brodie MJ. Epilepsy in elderly people. *Lancet* 2000; 355: 1441-6.

27. Hannah JA, Brodie MJ. Epilepsy and learning disabilities--a challenge for the next millennium? *Seizure* 1998; 7: 3-13.

28. Shorvon SD, Löwenthal A, Janz D, *et al*. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000; 41: 1179-86.

29. Cereghino JJ, Biton V, Abou-Khalil B, *et al*. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000; 55: 236-42.

30. Ben-Menachem E, Falter U, European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3000 mg/day in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000; 41: 1276-83.

31. Marson AG, Kadir ZA, Chadwick DW, *et al*. New antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997; 38: 859-80.

32. Kossoff EH, Bergey GK, Freeman JM, *et al*. Levetiracetam psychosis in children with epilepsy. *Epilepsia* 2001; 42: 1611-3.

33. Cramer JA, Ben Menachem E, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res* 2001; 47: 17-25.

34. Cramer JA, Fisher R, Ben-Menachem E, *et al*. New antiepileptic drugs: comparison of key clinical trials. *Epilepsia* 1999; 40: 590-600.

35. Zonisamide (Zonegran™). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 1307-11.

36. Gabapentin (Neurontin®). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 2655-9.

37. Topiramate (Topamax®). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 2590-5.

38. Lamotrigine (Lamictal®). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 1567-74.

39. Tiagabine (Gabitril®). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 1189-93.

40. Oxcarbazepine (Trileptal®). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 2407-12.

41. Levetiracetam (Keppra™). *Physicians' Desk Reference*. Montvale, NJ: Medical Economics Co, Inc, 2002: 3314-17.