REVIEW ARTICLE

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Benefit-Risk Assessment of Levetiracetam in the Treatment of Partial Seizures

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Contents

Abstract

Levetiracetam is a novel antiepileptic drug that has been demonstrated as being effective in the management of partial seizures. It is rapidly and completely absorbed after oral administration and it is predominantly eliminated as unchanged drug in the urine. Its metabolism is independent of the cytochrome P450 enzyme system, nor does it induce cytochrome P450 enzymes. As a result of its pharmacokinetic features, levetiracetam has not been demonstrated to interact with other drugs in either direction. In double-blind, placebo-controlled trials, all the levetiracetam dosages tested were effective, including 1000 mg/day, 2000 mg/day and 3000 mg/day. The ineffective dose is not known. Efficacy seemed to be maintained in long-term studies, with no evidence of tolerance.

In major double-blind, placebo-controlled trials discontinuation rates because of adverse events were 6.9–10.9% for levetiracetam-treated patients (all doses) compared with 5.3–8.6% for placebo-treated patients. The most common adverse events that differed between treatment groups and placebo control groups were somnolence, asthenia, dizziness and, in the US study, infection. Since levetiracetam was marketed, behavioural effects have been reported, namely irritability, agitation, anger and aggressive behaviour. These adverse effects are more likely in learning disabled individuals, those with prior psychiatric history and those with symptomatic generalised epilepsy. Overall, the risk has been estimated at 12–15%. Laboratory parameters overall seem to be not significantly affected by levetiracetam, although slight trends to lower white and red blood cell counts were detected in the studies. No organ toxicity has been described so far, with patient exposures exceeding 500 000.

In summary, levetiracetam exhibits a very favourable safety profile in patients with partial onset seizures. Whereas somnolence, asthenia and dizziness were the most prominent adverse effects in clinical trials, behavioural adverse effects have generally been the most common reason for drug discontinuation in clinical practice.

Epilepsy is a common condition that develops in approximately 1% of individuals by 20 years of age and approximately 3% by 70 years of age.[1] Epilepsy is characterised by recurrent, unprovoked seizures, which are the clinical manifestations of an abnormal electrical discharge of cortical neurons. The vast majority of seizures are self limited. Rarely, seizures do not stop, which leads to the condition of status epilepticus. Seizures are currently classified based on clinical and electrographic features into partial or generalised categories.[2] Partial seizures start in one part of one hemisphere, whereas generalised seizures seem to start simultaneously bilaterally. Partial seizures are subdivided into simple partial if consciousness is preserved or complex partial if consciousness is impaired. Partial seizures can also become secondarily generalised. Generalised seizure types include generalised absence, myoclonic, clonic, tonic, tonic-clonic or atonic seizures.

Partial seizures are the most common seizure type. Partial seizures may also be more likely to be

resistant to medical therapy. Approximately one-third of patients with epilepsy declare themselves refractory to medical therapy.[3] In addition, many patients are unable to tolerate some antiepileptic drugs (AEDs). This has fueled a search for new drugs that are better tolerated, have better pharmacokinetics and are more effective than classical AEDs or at least are effective where classical AEDs have failed. In the past decade, several new AEDs have been marketed in the US. Levetiracetam has been marketed since April 2000. It is now estimated that close to 1 million patients have been exposed worldwide. Levetiracetam is a pyrrolidine derivative (figure 1); it is the first drug in its family to be marketed for the treatment of seizures.

1. Pharmacokinetics

1.1 Adults

Levetiracetam has a number of favourable pharmacokinetic properties.[4,5] Absorption of levetiracetam is rapid and complete, with peak plasma concentrations (C_{max}) approximately 1 hour following oral administration. Coadministration with food does not affect the bioavailability, but reduces the C_{max} by 20% and delays it by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500–5000mg.[6] Protein binding at <10% is not clinically relevant. Levetiracetam is only partially metabolised in the blood, with hydrolysis of the acetamide group. The resultant metabolite is inactive. The metabolism is not dependent on the liver cytochrome P450 enzyme system. Levetiracetam plasma half-life in adults is 7 ± 1 hours. The half-life is 2.5 hours longer in the elderly.[7] Levetiracetam is eliminated by the kidneys, predominantly as unchanged drug (66%). Levetiracetam clearance is reduced in patients with impaired renal function and requires dose adjustment.[7] Levetiracetam and its most important metabolite do not affect hepatic microsomal enzymes and, therefore, are unlikely to interact with other drugs.[8] The absence of protein binding also makes interactions resulting from competition for protein binding unlikely. Pharmacokinetic interactions with phenytoin, warfarin, digoxin and oral contraceptives were not noted in clinical and pharmacokinetic studies.[4,5,9-14] Only two studies suggested a modest effect of enzyme-inducing AEDs on levetiracetam concentrations.[15,16]

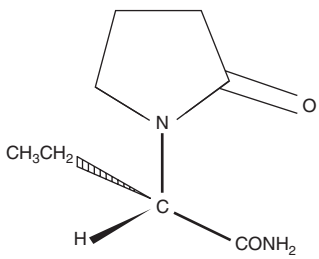

Fig. 1. Structure of levetiracetam.

1.2 Children

Pharmacokinetics in children were studied in 15 boys and 9 girls aged 6–12 years who received a single dose of levetiracetam (20 mg/kg) as an adjunct to their stable regimen of a single concomitant AED.[17] The half-life was 6 ± 1.1 hours. The C_{max} and area under the concentration-time curve were lower in children than in adults, and renal clearance was higher. The apparent body clearance was 1.43 ± 0.36 mL/minute/kg and was 30–40% higher in children than in adults.

2. Clinical Efficacy of Levetiracetam in Partial Seizures

2.1 Pivotal Trials in Adults

Levetiracetam efficacy was evaluated in three randomised, double-blind, placebo-controlled clinical trials, all of which demonstrated efficacy of all three tested levetiracetam dosages (table I). The first trial conducted in the US (study N132) compared two different dosages of levetiracetam, 500mg twice daily and 1500mg twice daily, and placebo orally as adjunctive treatment in patients with partial seizures.[18] 294 patients were randomised; 268 of them completed the 14-week treatment. During a 12-week single-blind baseline period, each patient received baseline AEDs and placebo twice daily and all seizures were counted. Titration of the experimental treatment was then started. The levetiracetam dose was escalated at 2-week intervals during 4 weeks of titration. Patients assigned to the 1500mg twice daily dosage were given 500mg twice daily

Table I. Efficacy data from three double-blind, controlled studies of levetiracetam in patients with partial seizures

Study	Drug and daily dose (mg)	No. of patients	Median % reduction in seizure frequency relative to baseline	Mean % seizure reduction over placebo	50% responder rate (%)	Seizure free rate (%)
Cereghino et al.[18]	Levetiracetam 1000	98	32.5	20.9	33.0[a]	3.1
	Levetiracetam 3000	101	37.1	27.7	39.8[a]	7.9[b]
	Placebo	95	6.8	NA	10.8	0
Shorvon et al.[21]	Levetiracetam 1000	106	17.7[a]	16.4[b]	22.8[c]	5
	Levetiracetam 2000	106	26.5[a]	17.7[b]	31.6[a]	2
	Placebo	112	6.1	NA	10.4	0.9
Ben-Menachem	Levetiracetam 3000	181	39.9[a]	32.7	42.1[a]	8.2[c]
and Falter[22]	Placebo	105	7.2	NA	16.7	1

a $p < 0.001$ vs placebo.

b $p < 0.01$ vs placebo.

c $p < 0.05$ vs placebo.

NA = not applicable.

for 2 weeks, 1000mg twice daily for 2 weeks, then 1500mg twice daily. The patients randomised to the 500mg twice daily dosage first received one-third and then two-thirds of the dosage (167mg twice daily, then 333mg twice daily). The treatment period lasted 14 weeks. Concomitant AEDs were kept at the same dose throughout the trial. The median percent seizure reduction in comparison with baseline was 6.8% for the placebo group, 32.5% for the levetiracetam 1000 mg/day group and 37.1% for the levetiracetam 3000 mg/day group. The 50% responder rate was 10.8% for placebo, 33.0% for levetiracetam 1000 mg/day and 39.8% for levetiracetam 3000 mg/day. Seizure freedom was noted in 3 of 98 patients in the levetiracetam 1000 mg/day group, 8 of 101 patients in the 3000 mg/day group and 0 of 95 patients in the placebo group. The difference between levetiracetam 3000 mg/day and placebo was significant ($p = 0.01$). The maximum efficacy of levetiracetam was already present at week 2 of the maintenance period. In fact, in subsequent analyses of time to initial therapeutic effect,[19] maximal efficacy was already present at the first visit following initiation of titration for both the 1000 mg/day and 333 mg/day dosages, and a statistically significant change in daily proportion of seizure-free patients was noted the first day of treatment with 1000 mg/day.[20]

In the European randomised, double-blind, placebo-controlled, multicentre trial (study N051), 324 patients were randomised to treatment with either placebo (112 patients), levetiracetam 1000 mg/day (106 patients) or levetiracetam 2000 mg/day (106 patients).[21] All enrolled patients entered a baseline period, which was initially 12 weeks but was then reduced to 8 weeks after a protocol amendment. At the end of baseline, patients randomised to levetiracetam 1000 mg/day received placebo for 2 weeks, then levetiracetam 500mg twice daily. Patients randomised to 2000 mg/day received 500mg twice daily for 2 weeks and 1000mg twice daily thereafter. The titration period lasted for 4 weeks and was followed by a maintenance phase of 12 weeks, during which time the levetiracetam dose did not change. Concomitant AEDs were kept constant throughout the study. 228 patients completed the study. Levetiracetam significantly decreased seizure frequency in comparison with placebo for both test-

ed dosages. There was a 6.1% median seizure reduction from baseline for the placebo group, 17.7% for the levetiracetam 1000 mg/day group and 26.5% for the levetiracetam 2000 mg/day group. The difference between the two dosages of levetiracetam was not statistically significant, and there was no significant difference in the response of different seizure subtypes. When the 50% responder rate was examined, a significant difference was again found between placebo and the treatment groups, with 22.8% of responders for levetiracetam 1000 mg/day, 31.6% of responders for levetiracetam 2000 mg/day and 10.4% of responders for the placebo group. Again, there was no significant difference in the responder rate between the dosages of levetiracetam. Five of 106 (5%) patients in the 1000 mg/day group, 2 of 106 (2%) in the 2000 mg/day group and 1 of 112 (0.9%) in the placebo group were seizure free (the seizure-free patient in the placebo group withdrew at day 29 but had been seizure free before that).

In a third study, also conducted in Europe (study N138), 286 patients were randomised to levetiracetam 3000 mg/day (181 patients) or placebo (105 patients).[22] Patients randomised to levetiracetam received 500mg twice daily at randomisation, 1000mg twice daily 2 weeks later and then 1500mg twice daily at the end of the 4-week titration period. After the final titration, patients entered a 12-week maintenance phase. The median partial seizure frequency was decreased significantly from baseline in patients treated with levetiracetam compared with placebo (39.9% vs 7.2%; $p < 0.001$). The 50% responder rate was also significantly higher with levetiracetam. A total of 42.1% of levetiracetam-treated patients were responders compared with 16.7% of placebo-treated patients; 8.2% (14 of 171) of levetiracetam-treated patients were seizure free during the maintenance phase in comparison with 1% (1 of 102) in the placebo group ($p = 0.012$). The number needed to be treated to find a 50% responder was 3.9 and to find a seizure-free patient was 13.9. Of note is that this study was followed by monotherapy conversion for responders (see section 2.3.2).

The pivotal study results were subsequently reanalysed by meta-analysis to evaluate seizure-free days. The analysis computed the seizure-free days gained per quarter compared with placebo. In the treatment period incorporating the titration period, the meta-analysis results showed a statistically significant gain in seizure-free days for each levetiracetam dosage. The gain was 4.38 days per quarter for levetiracetam 1000 mg/day, 5.51 days per quarter for levetiracetam 2000 mg/day and 5.63 days per quarter for levetiracetam 3000 mg/day.[23]

2.2 Pivotal Trial in Children

A large double-blind, placebo-controlled, multicentre add-on trial of levetiracetam was carried out in children aged 4–16 years with refractory partial onset seizures. This study has only been published in abstract form.[24] Of 216 randomised patients, 198 had evaluable data: 101 received levetiracetam and 97 received placebo. Levetiracetam was started at 20 mg/kg/day and titrated over 6 weeks up to 60 mg/kg/day. There was a highly significant difference between levetiracetam and placebo in the primary endpoint ($p = 0.002$), with a 26.8% reduction in seizure frequency for levetiracetam over placebo. The 50%, 75% and 100% responder rates for patients receiving levetiracetam were 44.6%, 19.8% and 7%, respectively, compared with 19.6%, 5.1% and 1% for patients receiving placebo. The adverse event profile was similar to that noted in adults, with somnolence being the most common adverse event.

2.3 Other Blinded and Placebo-Controlled Trials

Other placebo-controlled trials of levetiracetam were either extensions of the pivotal studies mentioned in sections 2.1 and 2.2 or were predominantly designed for efficacy analysis. They are listed as follows according to the specific efficacy aspect they addressed.

2.3.1 Dosage-Response Effect of 1000 and 2000 mg/day

As an extension of the first European trial (study N051),[21] patients were enrolled in a blinded crossover extension that involved treatment of each group with either of the two other treatments.[25] Thus, the patients initially randomised to placebo subsequently received either levetiracetam 1000 mg/day or levetiracetam 2000 mg/day; the levetiracetam 1000 mg/day group received either levetiracetam 2000

mg/day or placebo; and the 2000 mg/day group received either levetiracetam 1000 mg/day or placebo. Both levetiracetam dosages were superior to placebo in weekly seizure frequency. Comparison of the two dosages of levetiracetam did not reveal a difference in weekly seizure frequency. However, a within-patient comparison in the 93 patients who received both dosages of levetiracetam during the trial revealed a significantly greater 50% responder rate for those receiving 2000 mg/day than for those receiving 1000 mg/day ($p = 0.018$), regardless of the sequence of administration. The odds of a patient becoming a responder while receiving 2000 mg/day was 4.2% higher than for a patient receiving levetiracetam 1000 mg/day.[25]

2.3.2 Monotherapy

The study design of the third pivotal add-on study (study N138) included a late phase following completion of the add-on evaluation phase, in which patients who responded well (defined by several criteria including 50% reduction of complex partial seizures) during the add-on evaluation phase were eligible for entry into a monotherapy phase where the concomitant AED was tapered.[22] The concomitant AED was withdrawn gradually during a period of up to 12 weeks, while the study medication remained constant. This concomitant AED withdrawal phase was followed by a 12-week monotherapy phase, with levetiracetam or placebo. Patients were withdrawn from monotherapy if they met one of three escape criteria: (i) doubling of complex partial or secondarily generalised seizure frequency; (ii) status epilepticus; or (iii) occurrence of generalised tonic-clonic seizures if none had occurred during baseline. Overall, 19.9% of patients randomised to levetiracetam treatment completed the study compared with only 9.5% of patients randomised to the placebo group ($p = 0.029$). Of 239 patients who completed the add-on phase, only 86 patients were eligible for monotherapy conversion. They included 69 levetiracetam-treated patients and 17 placebo recipients. Monotherapy conversion was successful in 49 levetiracetam-treated patients. In these patients, there was a significant seizure reduction compared with baseline, but seizure frequency was slightly higher than in the add-on phase. The responder rate among the 49 patients was 59.2%, with nine seizure-free patients. Six of these nine patients were seizure free from the time of titration. It was not possible to determine how many of the patients who were seizure free while receiving combination therapy had seizure recurrence during or after conversion to monotherapy. The placebo group was difficult to analyse because eight patients were switched to levetiracetam for 'ethical' reasons but were still counted as placebo patients. This study suggested that levetiracetam monotherapy could be considered for some patients with refractory partial epilepsy and that efficacy, including complete seizure control, could be maintained after monotherapy conversion.

2.3.3 Efficacy of Levetiracetam 4000 mg/day

In one study that was mainly planned for evaluation of tolerability of levetiracetam, 119 patients were randomised to placebo, levetiracetam 2000 mg/day or levetiracetam 4000 mg/day.[26] Patients were started on the full dose, without any titration. The main efficacy assessment was a 50% responder rate. The responder rate was 48.1% in the 2000 mg/day group but, unexpectedly, only 28.6% in the 4000 mg/day group, compared with 16.1% in the placebo group. The difference in response was significant only between the 2000 mg/day and the placebo groups. Although this study was not powered for differences between the levetiracetam groups, it clearly suggested that 4000 mg/day did not have any advantage over 2000 mg/day and may even have had a relative disadvantage in regard to efficacy. Of note is that the study included not only patients with partial onset seizures but also patients with generalised epilepsy (46% of patients). Close to 50% of patients were in the partial onset group.

2.4 Open-Label Studies

A number of published open-label studies have confirmed the efficacy of levetiracetam. These studies were mostly performed after the pivotal trials, but some were earlier trials. Open-label studies have reflected the efficacy of levetiracetam demonstrated in double-blind studies, although changes in seizure frequency and responder rate values were often more impressive than in double-blind studies. The open-label studies often added useful information regarding the pattern of efficacy of levetiracetam.

Selected studies are presented in relation to specific contributions.

2.4.1 Lowest Effective Dose

In one early study, 17 patients completed 4 weeks of baseline placebo treatment, then entered a 16-week active treatment period with ascending dosages of levetiracetam, from 500 mg/day to 2000 mg/day.[27] The dose was increased by 500mg every 4 weeks according to tolerability. Of the 14 patients who completed the trial, six were >50% responders. A significant decrease in simple and complex partial seizures was achieved by levetiracetam 500 mg/day ($p < 0.03$), which suggested that this was an effective dose. The lowest dosage of levetiracetam tested in the pivotal trials was 1000 mg/day, although *post hoc* analysis of the titration period suggested that as little as 333 mg/day was effective in the first 2 weeks of titration.

2.4.2 Dose-Effect Relationship

A dose escalation study enrolled 29 patients with refractory epilepsy at three centres.[28] All patients entered a 4-week baseline phase (single-blind placebo). After the baseline phase, patients were either in open-label treatment or single-blind treatment. The initial dosage, added to existing AEDs, was levetiracetam 1000 mg/day for 2 weeks, which was increased to 2000 mg/day for 2 weeks, 3000 mg/day for 4 weeks, then 4000 mg/day for 4 weeks. Levetiracetam was effective at all dosages, without a clear dose-effect relationship. Median seizure frequency decreased from 2.06 seizures/week during baseline placebo treatment to 1.0 seizure/week on treatment with 1000 mg/day, 1.5 seizures/week on 2000 mg/day, 1.0/week on 3000 mg/day and 0.75/week on 4000 mg/day. The difference from placebo was statistically significant for the 1000 mg/day and the 4000 mg/day dosages.

2.4.3 Individualised Doses

Levetiracetam was evaluated in a 10- to 16-week open-label, multicentre study in 219 adult patients with epilepsy (183 had partial epilepsy, 37 had generalised epilepsy and 1 had both) refractory to at least two AEDs.[14] Titration was flexible with respect to the eventual maintenance dosage, allowing patients to be receiving 1000 mg/day, 2000 mg/day or 3000 mg/day, depending on seizure response and tolerability. Concomitant AEDs and their doses were not changed during the study. In total, 81.7% (179 of 219) of patients completed the study and 78.5% (172 of 219) chose to continue levetiracetam in a follow-up study. The ≥50% responder rate was 48.2% for all seizure types, 49.4% for partial onset and 51.4% for generalised onset seizures. Twenty-six patients (13.6% of 191 who completed titration and entered maintenance) were seizure free. The higher responder rates compared with those achieved in the pivotal trials (see table I) reflected both that the patient population in this trial was less refractory than in the pivotal trials and that the flexibility of individualised doses allowed patients to stop at their effective best-tolerated dose.

Another more recent Australian study also utilised individualised dosages in 99 enrolled patients with partial onset seizures. Add-on levetiracetam reduced the weekly frequency of partial onset seizures by a median of 35.9%. The 50% responder rate in this study was 42.4%.[29]

In another single-centre observational study, 156 patients with uncontrolled partial or generalised epilepsy received adjunctive levetiracetam at a flexible dosage. Forty-seven percent of patients were ≥50% responders, including 26% who became seizure free. Most (63%) of the seizure-free patients took a dosage of ≤1000 mg/day.[30]

2.4.4 Community-Based Patients

A large, predominantly community-based, phase IV, prospective open-label study (KEEPER™ trial) enrolled 1030 patients with partial onset seizures who were having at least one partial seizure per month.[31] Levetiracetam 500mg twice daily (or 250mg twice daily in the presence of moderate renal impairment) was added to existing AEDs. Dose titration was continued up to 1500mg twice daily by the fourth week of titration. Patients who were free of seizures at the initial or subsequent dose did not have their regimen changed. After a 4-week dose adjustment period, patients entered a 12-week dose evaluation period. 747 patients completed the entire study. The overall median reduction in partial seizure frequency was 62.3%. Among patients who provided efficacy data, 57.9% of patients experienced at least a 50% reduction and 40.1% at least a 75% reduction in seizures during the 16 weeks of the trial. Twenty percent of patients (187 of 936) were

seizure free. Responder rates were higher for patients taking one or two concomitant AEDs than for those entering the trial taking three AEDs.

2.4.5 Efficacy in the Elderly

A subset of 78 KEEPER™ trial patients aged ≥65 years were identified and analysed separately.[32] The completion rate in this subgroup was 73.1% (57 patients), equivalent to the overall completion rate of 72.5%. The mean baseline partial seizure frequency in the subgroup was 3.3 seizures per month. Most patients (52.6%) received levetiracetam 1000 mg/day, 20.5% received 2000 mg/day and 19.2% received 3000 mg/day as their maximum dosage. The median percentage reduction in partial seizures was 80.1%. Overall, 76.9% were >50% responders, 56.9% were >75% responders and 40% were seizure free during the 16 weeks of the study. Levetiracetam was also well tolerated in this group (see section 5.10). Therefore, there seemed to be greater levetiracetam efficacy in the elderly than other age groups in the KEEPER™ trial.

2.4.6 Relationship Between Age at Onset and Levetiracetam Efficacy

One retrospective study involved medical record review of patients with refractory epilepsy treated with levetiracetam and identified those who were seizure free, had improved seizure control (by ≥50%) or had worsened seizure control.[33] These three groups included 44 patients; those who had <50% improvement were not considered. The investigators found that those who responded well to levetiracetam were older at the onset of epilepsy than those who did not (mean age 51 years vs 27 years). This was also true of the subset of patients who specifically had localisation-related epilepsy. This is not totally surprising, as epilepsy in the elderly has been previously noted to be fairly responsive to treatment in general.[34]

2.4.7 Monotherapy in the Elderly

One retrospective postmarketing study in patients with a confirmed diagnosis of epilepsy aged ≥60 years identified 14 patients who were given levetiracetam as first-line therapy or were converted to levetiracetam monotherapy after prior AEDs had failed.[35] Eight of these patients were diagnosed with epilepsy after the age of 60 years. Overall, eight patients became seizure free, including four of five patients who started levetiracetam as first-line therapy. Dizziness was the only adverse event reported and did not require treatment discontinuation.

2.4.8 Monotherapy in Newly Diagnosed Partial Epilepsy

One small retrospective study identified 13 patients treated with levetiracetam as first-line therapy.[36] Two discontinued treatment because of adverse experiences (specifically irritability). The remaining 11 continued treatment for at least 6 months and were all responders, including six who were seizure free.

2.4.9 Conversion to Monotherapy

One retrospective report of levetiracetam monotherapy included 28 patients converted to monotherapy after at least one AED failed.[37] Nine patients (32%) became seizure free and 12 others had at least a 50% improvement, resulting in a 75% overall responder rate.

2.4.10 Seizure Localisation and Levetiracetam Efficacy

There are no studies focused on evaluating the efficacy of levetiracetam in relation to localisation. However, one study that evaluated age at onset in levetiracetam responders also evaluated localisation in responders and in patients who had worsening of seizures.[33] Patients who had temporal lobe epilepsy were more likely to do well (0 worse, 9 improved, 4 seizure free) than those with frontal lobe epilepsy (2 worse, 0 improved, 2 seizure free).

2.4.11 Efficacy in Patients who have Failed Surgery

A retrospective analysis of levetiracetam in patients with refractory partial epilepsy included 82 patients, 21 of whom had undergone epilepsy surgery that had failed.[38] The responder rate was significantly better in patients with failed epilepsy surgery. Among these patients, 76.1% were 50% responders, including 47.6% (10 of 21) who became seizure free. Those with failed temporal lobe surgery were most likely to benefit (11 of 12 were responders after failed temporal lobe surgery and 5 of 9 after surgery outside the temporal lobe). The responder rate in those who did not have surgery was 34.3%, including 14.7% (9 of 61) who became seizure free. This study suggested that levetiracetam therapy should be considered early after failed temporal lobe surgery. In another study of 86 patients

who had persistent seizures after temporal lobectomy, five of seven patients who received levetiracetam postoperatively became seizure free. Newly administered levetiracetam showed a significant positive effect on the postoperative outcome in patients for whom surgery had failed, independent of other prognostic factors.[39] Thus, levetiracetam seems particularly effective in this patient group with residual postoperative seizures.

2.4.12 Efficacy in Children

The only published efficacy studies in children have been open-label studies. These indicate good efficacy, which is not clearly different from adults.

In one prospective study, 23 children with refractory partial seizures receiving one standard AED were treated with levetiracetam after a 4-week baseline period.[40] Levetiracetam was titrated over 6 weeks to a target dosage of 40 mg/kg/day. However, the levetiracetam dosage was individualised in a range of 20–40 mg/kg/day. Twelve children (52%) had their seizure frequency reduced by >50%. Two patients remained seizure free. The reductions in seizure frequency were greatest for secondarily generalised seizures (mean 45.9% and median 64.0% compared with 29.8% and 53.0% for all partial onset seizures).

Some reports have addressed the efficacy of levetiracetam at the syndrome level. In one prospective study, 21 children with a variety of syndromes were enrolled.[41] The starting dosage was 10 mg/kg/day and was increased every fourth day by 10 mg/kg/day up to a maximum of 60 mg/kg/day, depending on efficacy and tolerability. In this highly refractory population, 47% showed a ≥50% reduction in seizure frequency and levetiracetam was effective in both partial and generalised seizures and a variety of syndromes. However, there was particular efficacy in myoclonic seizures and associated syndromes, where 64% of patients (7 of 11) were responders. In addition to this study, there are small case series and case reports demonstrating efficacy in specific syndromes. In six children with Lennox-Gastaut syndrome, levetiracetam was effective for some patients in reducing or eliminating myoclonic, tonic-clonic and, to a lesser extent, atonic seizures.[42] Tonic seizures were not helped. Levetiracetam was highly effective in one patient with Landau-Kleffner syndrome,[43] and in two of three patients with the related syndrome of continuous spikes and waves during slow sleep.[44]

In another study that included adults and children,[45] 99 patients (64 with partial epilepsy and 35 with generalised epilepsy) with a mean age of 14 years (range 1–32 years) received levetiracetam add-on therapy that started at 10 mg/kg/day with 5-day increments up to 50 mg/kg/day or the maximum tolerated dosage. Concomitant AEDs were not modified. At last follow-up, 11 patients, all with partial epilepsy, were seizure free. Fourteen patients had >75% improvement and eight had >50% improvement. Overall, 40.6% of partial epilepsy patients were responders, compared with 20% of patients with generalised epilepsy. Seizures were unchanged in 38 and worsened in 23 (20.3% of patients with partial epilepsy and 28.6% of those with generalised epilepsy). Although patients with both partial and generalised epilepsy benefitted, greater benefit was noted in patients with partial epilepsy.

Other retrospective reviews have confirmed the efficacy of levetiracetam in partial epilepsy but differed with respect to generalised seizure types. In one study, 39 children (mean age 8.6 years) with a variety of epileptic syndromes were treated with levetiracetam for up to 9 months.[46] Overall, 33% of patients were responders and 7.7% were seizure free. Levetiracetam was most effective for partial onset seizures with >50% being responders. Another retrospective study evaluated 26 children aged ≤10 years with both partial or generalised epilepsy.[47] Levetiracetam appeared most effective in children with partial onset seizures. Overall, 61% of patients were 50% responders and two patients were seizure free.

2.4.13 Efficacy in Idiopathic Generalised Epilepsy

Although this paper is focused on partial epilepsy, efficacy in generalised epilepsy has an impact on the treatment of patients in whom epilepsy cannot be clearly classified as partial or generalised, or patients who have both partial and generalised onset seizures. Preliminary evidence from predominantly retrospective open-label data suggests that levetiracetam has a wide spectrum of efficacy, as suggested in several of the papers discussed in section

2.4. A very early study supported efficacy of single levetiracetam doses in suppressing photosensitivity, which is usually related to idiopathic generalised epilepsy.[48] One study specifically examined the efficacy of levetiracetam in refractory idiopathic generalised epilepsy.[49] Levetiracetam was effective in several generalised seizure types and idiopathic generalised epileptic syndromes, but particularly so in myoclonic seizures, generalised tonic-clonic seizures and juvenile myoclonic epilepsy. Other small reports also suggest levetiracetam efficacy and the need to explore this in large formal trials.[50-52]

2.4.14 Paradoxical Increase in Seizures

Some of the studies discussed previously reported that some patients had an increase in seizures. A paradoxical increase in seizures was particularly noted at elevated doses. In one study that focused on this effect, levetiracetam was examined as an add-on treatment in 78 adults and 44 children with intractable epilepsy.[53] A ≥50% reduction in seizure frequency was achieved in 40% of adults and 20% of children, and 9% of adults and 7% of children became seizure free. However, in 18% of adults and 43% of children, levetiracetam was associated with a >25% increase in seizure frequency. This was more likely in mentally retarded patients and at relatively high doses. On the other hand, one paediatric study reported that seizure worsening, which occurred in 23% of patients, was generally reported early in the titration phase.[45]

2.5 Long-Term Studies

Short-term efficacy has to be confirmed with long-term efficacy data. Long-term efficacy can be assessed with retention rate, but long-term seizure freedom is the most meaningful measure. Long-term experience may differ from short-term experience in several ways. It could be better because of greater freedom in adjusting the dose and schedule or the opportunity of adding synergistic therapy. On the other hand, it could be less favourable, as patients may lose patience with adverse effects that they would otherwise tolerate for short periods of time. The long-term experience could also be less favourable if tolerance develops to the therapeutic effect. One report of tolerance developing during long-term levetiracetam treatment of kindled rats made this issue even more important.[54] Long-term levetiracetam studies have included data for patients exposed to levetiracetam during the development programme, as well as patients treated in the post-marketing period. Both demonstrated that the therapeutic efficacy of levetiracetam is retained for the majority of patients who respond.

During the development of levetiracetam, 1422 patients were exposed, most of them in four double-blind trials.[55] The median duration of treatment was 399 days with a range of 1–2984 days. Overall, there were 2421 patient years of exposure. As expected, considering that patients were in widely varying trials, the starting dosage varied from 250 mg/day to 4000 mg/day with a median of 1000 mg/day. The eventual daily dosage also varied from 250 mg/day to 5000 mg/day with a median of 3000 mg/day for adults, 2000 mg/day for the elderly and 1250 mg/day for children. At the cut-off date in this cohort, 39.5% of patients were still treated. The continuation rate was 60% after 1 year, 37% after 3 years and 32% after 5 years.[55] However, most discontinuations were not because of adverse effects or lack of efficacy, but rather a result of administrative study-related reasons such as protocol violations, withdrawal of consent or end of a study. Withdrawals because of adverse events constituted 15.8% and those resulting from lack of efficacy constituted 18.4%. When the factors predicting levetiracetam continuation were examined, the ones that were found to be significant were a high maximal dose, a low starting dose, the presence of generalised seizures and a smaller number of AEDs at baseline. Thirteen percent of patients became seizure free for at least 6 months during the study. Eight percent were seizure free for at least 1 year and 4.5% became seizure free from the first day of exposure and remained seizure free until the cut-off point.

The same cohort of patients were assessed with a different analysis, evaluating patients who were treated for at least 6, 12, 18, 24, 30, 36, 42, 48 and 54 months.[56] The overall median percent reduction of seizures was 39.6%. There was no decrease in the median percent reduction within each cohort. For the group exposed for 54 months, the median percent reduction was highest, as would be expected.

That median percent reduction appeared to increase rather than decrease over time. The proportion of responders overall was 39% in the first 3 months, 36.1% at 6 months and 41% for the last 6 months of follow-up. During the last 6 months of treatment, 11.7% of patients were seizure free overall. Patients who were taking a single adjunctive AED did better, with 19.8% seizure free during their last 6 months. The stability of response was evaluated by examining the percentage of responders in the first 3 months who remained responders in the subsequent 3 months and the percentage of the latter who remained responders in the next 3 months.[57] In the first 3 months, 73.6% of the responders remained responders in the next 3 months and 82% of those were still responders in the subsequent 3 months. The subgroup of 491 patients who took levetiracetam plus one concomitant AED was further analysed. Of those patients, 40.4% were 50% responders and 22% were 75% responders overall. In the last 6 months, 43.1% were 50% responders and 29.1% were 75% responders. These data strongly suggest that levetiracetam response was maintained.

Several studies evaluated long-term efficacy of levetiracetam after marketing.[57-60] In clinical practice, more treatment-naive patients are expected to participate and these patients may be less willing to withstand adverse effects. In addition, inclusion of more patients with psychiatric and medical co-morbidity (who may not be allowed in trials) may result in a larger number of withdrawals from adverse experiences. The retention rates in four studies at 1 year varied from 61% to 77%.[57-60] The 1-year seizure-free rate varied from 16% to 26%. In one study, 32% of 120 patients were seizure free at 6 months and 26% were seizure free at 1 year.[58] Among those patients who were seizure free at 6 months, 74% were still seizure free at 1 year and another 18% were >90% improved at 1 year. In one study where the duration of follow-up varied from 1 to 2 years, the retention rate was 72.1% at last follow-up.[57] Over the last year, 11.6% were seizure free and 19.1% were 90% responders. The median levetiracetam dosage was less in seizure-free patients than in non-responders (1704 mg/day vs 2333 mg/day). The stability of response was assessed by evaluating the first 3 months of treatment versus the last 3 months of treatment. Of those patients who were seizure free at 3 months, 81.5% were still seizure free in the last 3 months of treatment. However, 39% of those who were seizure free at last follow-up were not seizure free at 3 months, which indicated that they became seizure free with additional medication adjustment.

It should be noted that most of these long-term studies included patients with both partial epilepsy and generalised epilepsy, although partial epilepsy always constituted the majority of patients.

3. Mechanisms of Action of Levetiracetam

Mechanism of action has limited value in the benefit-risk assessment, because it is likely that we are not aware of all mechanisms of action. However, the absence of mechanisms known for other AEDs and the presence of unique mechanisms may influence the use of the drug in certain circumstances. Levetiracetam has a unique profile in animal models of epilepsy. Unlike other AEDs, levetiracetam is not effective in acute models of epilepsy (used traditionally to screen new AEDs).[61,62] On the other hand, levetiracetam is effective in chronic epilepsy models.[62] It is also effective in counteracting the development of amygdala electrical kindling.[63,64] Although this suggests the potential for antiepileptogenic effects, its relevance to human epilepsy is unknown and there has been no study to date that has addressed this potential effect in humans. At the molecular level, levetiracetam does not share some of the more important established mechanisms of action of other AEDs, including blockade of voltage-dependent sodium channels and T-type calcium currents.[65] Levetiracetam failed to interact with GABA or glutamate receptors *in vitro*.[66] However, levetiracetam affected GABA transmission indirectly by reversing the inhibition of neuronal GABA- and glycine-gated currents by negative allosteric modulators, zinc and β-carbolines.[67] In addition, levetiracetam produced a partial depression of the N calcium current (neuronal high voltage activated calcium current).[68,69] Levetiracetam has a specific binding site in the CNS, which is reversible, saturable and stereoselective.[70] Recently, this binding site was determined to be the synaptic vesicle protein SV2A, which is involved in vesicle exocytosis.[71] This suggests that levetiracetam may influence

Table II. Withdrawal from three double-blind, controlled studies of levetiracetam in patients with partial seizures

Study	Drug and daily dose (mg)	No. of patients	Withdrawals because of adverse events (%)	All withdrawals (%)
Cereghino et al.[18]	Levetiracetam 1000	98	6.1	12.2
	Levetiracetam 3000	101	6.9	7.9
	Placebo	95	5.3	6.3
Shorvon et al.[21]	Levetiracetam 1000	106	7.5	11.3
	Levetiracetam 2000	106	14.2	17.9
	Placebo	112	5.4	13.4
Ben-Menachem and Falter[22]	Levetiracetam 3000	181	9.4	17.7
	Placebo	105	8.6	14.3

neurotransmitter release, but the specific effect of levetiracetam in that regard is not known.

4. Effect of Levetiracetam in Co-Morbid Conditions

Efficacy of AEDs in frequently encountered co-morbid conditions may affect the choice of an AED. As with other AEDs, levetiracetam has been tried, on a small scale, in a variety of conditions including migraine, tremor, myoclonus, pain, anxiety, bipolar disorder and autism. There is preliminary evidence of efficacy for levetiracetam in migraine, one of the most common co-morbid conditions.[72,73] Levetiracetam was effective in a several types of myoclonus,[74-82] but there was variable efficacy for tremor.[83-86] There was a partial or full response to levetiracetam in six of ten patients with postherpetic neuralgia[87] and an encouraging response in three patients with neuropathic pain.[88] Levetiracetam seemed helpful in phasic but not tonic spasticity in a group of patients with multiple sclerosis.[89] There is a suggestion of potential benefit in anxiety,[90] acute mania,[91] rapid cycling bipolar disorder[92] and refractory bipolar disorder.[93] Several measures were improved in patients with autism.[94] Perhaps with the exception of myoclonus, additional data is needed before co-morbidity with any of these conditions is considered an indication for levetiracetam therapy.

5. Adverse Effects

5.1 Adverse Events in the Double-Blind, Placebo-Controlled Trials

Adverse events in the pivotal levetiracetam trials were predominantly mild and infrequently resulted in withdrawal from studies (table II and table III). In the US double-blind trial, the adverse event that was most likely to result in withdrawal was somnolence.[18] The overall incidence of adverse events did not seem to be different between placebo and treatment groups. However, certain specific adverse events were more likely in patients treated with levetiracetam than in those receiving placebo. Treatment-emergent adverse events that had a higher incidence with levetiracetam than with placebo were infection, headache, somnolence, dizziness, asthenia, rhinitis and flu syndrome. Accidental injury was more frequent in the placebo group. In the first European double-blind trial, somnolence, asthenia and headache were reported more often in patients who had received levetiracetam than in placebo recipients.[21] In the third double-blind study that took some patients to monotherapy, the overall incidence of adverse events was also comparable between treatment groups.[22] Adverse events that were more common in the levetiracetam group and had an incidence of >5% included asthenia, infection and somnolence, while accidental injury and headache occurred more often with placebo.

In a subsequent double-blind, placebo-controlled study that was mainly designed for assessment of tolerability, levetiracetam 2000 mg/day or 4000 mg/day was started without titration.[26] The incidence of adverse events was still similar among study groups. The most frequently reported adverse events were also somnolence and asthenia and the incidence of somnolence was highest in patients receiving levetiracetam 4000 mg/day (44.7%), but was comparable between the 2000 mg/day treatment group and the placebo group. Asthenia was most commonly reported by the 2000 mg/day group (31%) but was comparable between the 2000 mg/day treatment group and the placebo group (26.2%

Table III. Incidence of adverse events (%) during three double-blind, controlled studies of levetiracetam in patients with partial seizures

Drug and daily dose (mg)	Somnolence	Asthenia	Dizziness	Depression	Infection	Headache	Accidental injury	Reference
Levetiracetam 1000	20.4	16.3	17.3	<5	27.6	21.4	16.3	18
	9.4[a]	7.5[a]	4.7	1.9	9.4	13.2[a]	12.3	21
Levetiracetam 2000	11.3[a]	13.2[a]	6.6	5.7	6.6	16.0[a]	13.2	21
Levetiracetam 3000	18.8	12.9	19.8	<5	26.7	20.8	12.9	18
	6.1[a]	13.8[a]	<5	<5	7.2[a]	3.3	2.2	22
Placebo	13.7	11.6	7.4	<5	12.6	20	24.2	18
	4.5	8.0	3.6	2.7	6.3	8.9	15.2	21
	3.8	6.7	<5	<5	3.8	10.5[a]	9.5[a]	22

a Indicates significantly higher incidence compared with another treatment group (either levetiracetam > placebo or placebo > levetiracetam).

and 25.6%, respectively). Adverse events generally appeared within the first month of treatment and decreased during open-label treatment. In this particular study, withdrawals were comparable among treatment groups. Somnolence was the most commonly reported reason for discontinuation.

5.2 Adverse Effects Leading to Discontinuation in Long-Term Analysis of Patients Enrolled in Trials

The most common causes of withdrawal because of adverse experiences in 1422 patients were: convulsions (3.4%), somnolence (2%), asthenia (0.6%), depression (0.6%), dizziness (0.5%) and headache (0.5%).[55]

5.3 Changes in Laboratory Values

The safety profile of levetiracetam was systematically reviewed in all patients who were exposed to levetiracetam in the development programme.[95] There seemed to be slight, statistically significant but not clinically meaningful, reductions in red blood cell count, haematocrit ratio, haemoglobin level and white blood cell count for patients treated with levetiracetam in comparison with placebo controls.

5.4 Infections

Infections were more likely among levetiracetam patients (13.4% vs 7.5%), but these were mostly common colds and upper respiratory infections.[95] Patients who had an infection during treatment were more likely to have had an infection at baseline.

5.5 Allergic Reactions and Rashes

Among patients participating in double-blind, placebo-controlled trials, allergic reactions occurred equally in treatment and placebo groups.[95]

5.6 Behavioural Adverse Effects

Behavioural adverse effects were not noted to be an issue in the double-blind, placebo-controlled studies. However, behavioural adverse effects were noted in open-label studies and subsequent postmarketing analyses. The systematic review of levetiracetam safety mentioned previously[95] addressed

non-psychotic behavioural symptoms in all levetiracetam studies. The analysis found these symptoms in 13.5% of levetiracetam-treated patients with epilepsy versus 6.0% of placebo-treated patients with epilepsy.[95] Interestingly, this difference between levetiracetam- and placebo-treated groups was much smaller in cognition studies (6.3% vs 4.1%) and non-existent in anxiety studies (5.2% vs 5.5%). This suggested that behavioural adverse effects with levetiracetam were more likely in patients with epilepsy. It should be noted that patients in epilepsy studies received higher levetiracetam dosages (mean 2421 mg/day) than patients in the anxiety (mean dosage 516 mg/day) or cognitive studies (mean dosage 906 mg/day). Nevertheless, behavioural manifestations did not appear to be dose related upon statistical analysis. Behavioural problems during levetiracetam treatment were associated with a prestudy history of psychiatric problems. There was no difference in behavioural problems between treatment responders and non-responders.

In one systematic review focused on the behavioural effects of levetiracetam in patients treated during clinical trials,[96] behavioural events were again significantly more common among patients with epilepsy than patients treated with levetiracetam for cognition or anxiety. Affective symptoms occurring at a frequency of ≥1% in epilepsy patients treated with levetiracetam versus placebo included depression (3.8% vs 2.1%), nervousness (3.8% vs 1.8%), hostility (2.3% vs 0.9%), anxiety (1.8% vs 1.1%) and emotional lability (1.7% vs 0.2%).

Behavioural adverse effects were closely examined in one open-label study of levetiracetam at individualised dosages of between 1000 mg/day and 3000 mg/day.[14] Treatment-emergent behavioural adverse events noted in >5% of patients included nervousness (9.6%) and depression (7.3%). Less frequent behavioural adverse events were hostility (4.1%), personality disorder (3.7%), emotional lability (2.7%) and anxiety (2.3%). Psychosis, agitation, euphoria, suicide attempt and hallucinations occurred in <1% of patients (the first three adverse events occurred in two patients and the last two in one patient each). Most behavioural adverse events were mild or moderate in severity, but they were severe in 7 of 219 treated patients. Seven patients discontinued levetiracetam because of behavioural adverse events, including psychosis in two patients and attempted suicide, anxiety, depression, hostility and personality disorder in one patient each. Most behavioural adverse events did not require discontinuation of treatment.

Since marketing of levetiracetam, a number of studies have reported behavioural adverse effects and evaluated factors predicting these events. In one study, 30% of 184 adult patients who received levetiracetam had learning disabilities.[97] Significantly more behavioural adverse effects occurred in this group (23% vs 10% for those without learning disability). There was also a tendency towards fewer reported somatic CNS adverse effects in the learning disability group. Although behavioural problems seemed more frequent in the learning disabled patients, only four patients with learning disabilities stopped treatment because of behavioural adverse events. There was no relationship between maximum levetiracetam dose and behavioural adverse effects. In another study,[98] only 10.1% of patients treated with levetiracetam developed psychiatric adverse events. There was a significant association with previous psychiatric history, a history of febrile convulsions and a history of status epilepticus. Lamotrigine co-therapy had a protective effect. The authors also analysed a subgroup of this population: 118 patients with epilepsy and learning disabilities.[99] Psychiatric adverse events occurred in 12.7% of this subgroup. There was a significant association with a previous history of status epilepticus and previous psychiatric history.

Most often, behavioural adverse events are mild and do not require discontinuation but they are at times pronounced. In one study, 10 of 33 patients required levetiracetam dose reduction or discontinuation.[100] In a large case-controlled study,[101] 13% of 553 patients discontinued levetiracetam for any reason, including 7% who discontinued levetiracetam because of behavioural issues. Among the 38 patients who discontinued levetiracetam for behavioural adverse effects, 16 did so because of depression, 14 because of irritability, five because of aggression and three because of psychosis/hallucination. In univariate analysis, the patients who discontinued levetiracetam because of behavioural adverse events were more likely to have symptomatic

generalised epilepsy, a history of psychiatric diagnosis, faster titration rate to maximal dose of levetiracetam and lower maximal levetiracetam dose. In logistic regression analysis, the first three factors remained significant. A lower levetiracetam dose in the patients who discontinued levetiracetam was consistent with the notion that these patients were not able to tolerate a higher dose of levetiracetam.

In one long-term postmarketing study,[57] all of the 215 patients started on levetiracetam between April 2000 and August 2001 were evaluated. They had a minimum follow-up of 1 year. Behavioural adverse experiences were divided into categories. Irritability, agitation, inner feeling of aggression and moodiness were added together; 10.7% of patients were affected. Psychotic delusions occurred in only three patients and non-psychotic hallucinations in one patient. Delusions and hallucinations were reversed with levetiracetam discontinuation. Depression occurred in three patients and resolved spontaneously in two who continued to take levetiracetam. Psychiatric/behavioural adverse effects accounted for most discontinuations related to adverse experiences: 16 of 31 patients who discontinued levetiracetam because of adverse experiences or a combination of adverse experiences and lack of efficacy did so because of behavioural effects. The relationship between titration rate and behavioural adverse events was assessed since the authors changed the titration rate midway through the study. The incidence of behavioural effects did not change, suggesting that they were idiosyncratic. However, in an unpublished observation in the same patient group, there was improvement with dose reduction and with the passage of time when levetiracetam had been beneficial for seizures and the adverse experiences were not so severe as to require immediate discontinuation. After the passage of weeks to months, the dose of levetiracetam could be increased again slowly without recurrence of behavioural adverse events.

Behavioural adverse effects were reported with a higher incidence in paediatric series than with adults.[40,42,46] However, it should be noted that improvement in behaviour was also noted for some children. One study that reported behavioural adverse effects in 38.5% of 39 children (the category included aggression in 12.8%, sedation in 15.4% and hyperactivity in 10.3%) also reported improvement in behaviour and/or cognition in 25.6% of children after adding levetiracetam.[46] Another study of 77 children reported aggressiveness in 5% of children but improved behaviour in 22%.[102]

5.7 Psychosis

Psychosis may occur with many AEDs. There is no clear evidence of a specific association with levetiracetam. In addition to occasional patients reported in larger studies, there is one small case series of four children[103] and another single case report of psychosis.[104] In every case, there was reversal of symptoms with levetiracetam discontinuation. Four of five started within 1 month of initiation of treatment, but in one patient symptoms were delayed for 3 months after initiation of treatment. In one series of patients in whom epilepsy surgery had failed, 3 of 21 patients developed a delayed psychotic syndrome 4–9 months after initiation of treatment, each time requiring discontinuation.[38]

The guidelines published by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society did not list a specific association of levetiracetam with psychosis, but suggested that levetiracetam may be associated with the non-serious adverse effects of irritability and behaviour change.[105]

5.8 Quality of Life

It has been demonstrated that quality of life in epilepsy is very much influenced by adverse experiences, even more than by seizure control. Hence, this discussion is included with adverse experiences. In the US pivotal trial, a 31-item 'quality of life in epilepsy' questionnaire was completed by 246 patients at the end of baseline and at the 18-week follow-up visit.[106] Significant differences were found among the three treatment groups for 'seizure worry', 'overall quality of life' and 'cognitive functioning' domains in favour of the levetiracetam treatment groups compared with placebo. Treatment groups were not significantly worse in any domain. Responders had significant improvement in all areas, except 'medication effect', in comparison with non-responders. The presence of asthenia was asso-

ciated with significant changes in the 'emotional well-being' domain.

5.9 Effect on Weight

Levetiracetam appeared to have no significant effect on bodyweight and thus seemed to be weight neutral.[107]

5.10 Tolerability in the Elderly

The tolerability of levetiracetam in elderly patients aged ≥65 years was examined in all the patients who participated in clinical trials of anxiety and cognitive disorders, in comparison with younger individuals with anxiety and cognitive disorders and young patients with epilepsy.[108] The only significant differences were seen between young and elderly groups with anxiety disorders, in headache and tremor, which occurred slightly more often in the elderly. This suggested a generally favourable adverse event profile for levetiracetam in the elderly, who would otherwise be expected to have more adverse events than younger individuals.

In the KEEPER™ trial, the most common adverse experience in the age group of ≥65 years was somnolence, noted in 16.7% compared with 12.5% of those aged <65 years.[32] Other adverse experiences in order of incidence were dizziness (9%), confusion (3.8%), asthenia, anorexia, dyspepsia and accidental injury (all at 2.6%). Asthenia occurred in 8.8% in those aged <65 years. Most adverse experiences in the elderly were mild to moderate in severity. Somnolence occurred in 15% of patients taking <2 concomitant AEDs and in 22.6% of those taking ≥2 concomitant AEDs.

5.11 Teratogenicity and Safety During Pregnancy

Levetiracetam has been classified by the US FDA as a category C drug (to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus). The pharmacokinetic properties of levetiracetam, including the absence of an epoxide metabolite and the absence of enzyme induction, may predict a favourable profile. In addition, there are animal data supporting the absence of teratogenicity.[109] However, only limited data are available. Twenty-three women became pregnant while taking levetiracetam during clinical trials.[95] Since levetiracetam was an adjunctive treatment, no conclusions can be drawn regarding birth defects. In a short case series of three women with epilepsy who took levetiracetam as monotherapy, positive outcomes were reported for all three patients.[110] In another small report, there were no birth defects in 11 pregnancies with exposure to levetiracetam.[111] Low birthweight was noted in three of the infants; however, two of the these were exposed to other AEDs.[111] Normal birthweight was reported in another study of eight patients.[112] These studies are clearly insufficient to draw conclusions regarding the safety of levetiracetam in pregnancy. Results from a larger pregnancy registry will be necessary.

5.12 Safety During Breastfeeding

The low protein binding of levetiracetam predicts a high concentration of levetiracetam in breast milk. This was confirmed in a study of eight consecutive breastfeeding women taking levetiracetam. The mean maternal milk concentration was equal to that in serum. However, infant levetiracetam serum concentrations were very low, suggesting rapid elimination.[112]

5.13 Acute Poisoning

There is a single case report of acute levetiracetam poisoning with a dose of 30 000mg. The patient presented with obtundation and respiratory depression, but made a full recovery.[113]

5.14 Safety in Porphyria

The choice of AED in porphyria is limited because this condition is exacerbated by most of the classical AEDs. There is a single case report of successful treatment of hepatic porphyria with levetiracetam, without exacerbation.[114]

6. Pharmacoeconomic Considerations

All new AEDs are more expensive than old agents.[115] This will undoubtedly reduce their availability in many parts of the world, particularly developing and impoverished countries. However, for some of the classical AEDs there may be costs related to the monitoring of AED plasma concentrations, blood counts and liver enzyme levels. For

enzyme-inducing drugs there may be costs related to decreased efficacy of concomitant medications. Adverse experiences may be more common for some of the old AEDs and these also add to the financial burden of epilepsy medical care. Medication cost is only a portion of the total cost of medical care. For patients who continue to have refractory seizures there are expenses related to emergency room visits, hospital admissions and frequent clinic visits. For patients who become seizure free when a new AED such as levetiracetam is added, there may be overall cost savings.[116] Being able to determine efficacy rapidly may be a distinct pharmacoeconomic advantage of levetiracetam and may enhance cost savings for patients becoming seizure free.

7. Place of Levetiracetam in Therapy Compared With Other Antiepileptic Drugs

Based on class I evidence, levetiracetam is an effective add-on agent in the treatment of partial epilepsy in adults[117] and children.[24] However, there is class IV evidence that levetiracetam has a wide spectrum of efficacy that includes generalised seizure types. There are no studies directly comparing levetiracetam with other AEDs. Meta-analysis of controlled trials has been used for an indirect comparison.[118] This meta-analysis suggested that, as an add-on agent, levetiracetam combined favourable odds ratios for responder rate as well as for withdrawal from trials. Levetiracetam had a favourable 'responder-withdrawal ratio' in comparison with other agents.[118] This and features such as absence of drug interactions and a rapid onset of action suggest that levetiracetam may be used as a first or early add-on agent. Co-morbidities may influence the choice of the first add-on agent. For example, the presence of both obesity and migraine may favour the use of topiramate, whereas the presence of baseline irritability may favour the use of another agent with proven mood-stabilising effects. In the absence of a large controlled trial in new onset epilepsy, levetiracetam is not indicated as a first-line agent,[105] whereas the new agents lamotrigine, oxcarbazepine, gabapentin and topiramate have data supporting such use.[105] When conversion to monotherapy is indicated in patients with refractory partial epilepsy, there is not sufficient support for using levetiracetam at this time. Other new AEDs such as oxcarbazepine, lamotrigine and topiramate have greater support for this indication.[117]

8. Conclusions

Levetiracetam is clearly an effective AED as add-on treatment for partial epilepsy in adults, with recent pivotal data also demonstrating add-on efficacy in children. Formal blinded and controlled trials are still needed to support the use of levetiracetam as initial monotherapy and there is only limited data supporting conversion to levetiracetam monotherapy. The pharmacokinetic profile of levetiracetam is very favourable, with rapid absorption and a lack of interactions with other drugs. The most common adverse effects, somnolence, asthenia and dizziness, are generally mild and tend to improve over time. The most problematic adverse effects appear to be in the arena of behaviour (mostly irritability). These occur in <15% of patients. They seem to be idiosyncratic but, at the same time, they may be influenced by titration rate and dose in those patients who develop them. They are more likely in individuals with prior psychiatric difficulties and also seem more likely in those with learning disabilities. There is a suggestion that these may be more common in children and less common in the elderly. For patients whose behavioural adverse effects are mild, dose adjustment and the passage of time may alleviate or eliminate these manifestations.

The combination of efficacy data, favourable pharmacokinetics and a generally favourable adverse experience profile make levetiracetam an attractive agent for initial adjunctive therapy in adult patients with refractory partial epilepsy. A titration rate slower than that suggested by the pivotal trials should be used. Even slower titration and careful observation are indicated in individuals deemed at risk of developing behavioural adverse effects.

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