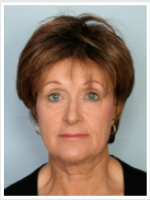
Research Review
PRODUCT REVIEW

An update on the use of Levetiracetam [Everet]

About the Reviewer



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After undergraduate training in medicine at the University of Tasmania, Elizabeth trained in neurology at Auckland Hospital. Postgraduate training consisted of an EEG/epilepsy Fellowship, followed by EMG training at the Mayo Clinic, Rochester Minnesota. She then returned to Auckland and has been a member of the Department of Neurology, as well as head of Clinical Neurophysiology and a member of the Epilepsy Surgical Group.

Elizabeth has had an active interest in epilepsy and helped to establish the national centre for surgical treatment of epilepsy at Auckland Hospital. The Epilepsy Surgical Group at Auckland Hospital, consisting of both adult and paediatric epileptologists, provides a tertiary referral service for surgical treatment of epilepsy in New Zealand, as well as providing a diagnostic service for patients with refractory epilepsy.

This review updates our 2011 review of levetiracetam [Levetiracetam-Rex], an established broad-spectrum second-generation antiepileptic drug (AED).

Levetiracetam-Rex now has a new brand name, Everet, which is approved for use in epileptic patients ≥6 years of age, as add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation.[1] This unchanged preparation with its new brand name now comes in a 1000 mg tablet in addition to the previously available doses.

As of the 1st of February 2016, Everet is available in New Zealand as 250 mg, 500 mg, 750 mg and 1000 mg tablets, fully subsidised by PHARMAC without the need for Special Authority.[1]

Epilepsy

Epilepsy, a common serious neurological disorder affecting both adults and children, is characterised by recurrent seizures.[2] Such seizures may be broadly categorised as either generalised (those occurring in and rapidly engaging bilaterally distributed networks) or focal (occurring within networks limited to one hemisphere and either discretely localised or more widely distributed).[3] Focal seizures are often referred to as partial seizures. Aetiologically, epilepsy is classified into four groups: idiopathic, cryptogenic, progressive and symptomatic.[4]

Incidence and prevalence

The incidence of epilepsy in developed countries is estimated to be approximately 50 cases per 100,000 people per year, with an estimated global prevalence of approximately 50 million; over half of these cases involve individuals with focal seizures.[5,6] In New Zealand, the epilepsy prevalence is about 0.6%, similar to that of other Western nations.[7,8] This equates to approximately 25,000 New Zealanders with active epilepsy at any one time.[8]

The burden of epilepsy

Epilepsy is associated with increased morbidity and mortality, including unexpected deaths without a clear cause, and accounts for 1% of the global burden of disease.[4,9,10] The World Health Organisation (WHO) estimated global rate of death due to epilepsy in 2004 was approximately 0.2%.[11]

Epilepsy consists of more than seizures for the affected individual and their family, having psychological, economic and social repercussions.[4] The dramatic and alarming clinical features of seizures frequently elicit fear and misunderstanding.[4] Within the wider community there is considerable ignorance about epilepsy and an unacceptable level of prejudice against individuals with the disorder.[7] Many patients with epilepsy are socially disadvantaged and often have difficulty obtaining jobs.[7] Individuals with epilepsy commonly encounter problems with driving, personal development, and social and personal relationships.[4] It is therefore not surprising that depression is a serious and frequent comorbidity of this condition.[12]

Diagnosis

An accurate diagnosis of epilepsy is fundamentally important, but confident diagnosis or exclusion is difficult because seizure types vary and there may be no accompanying neurological signs.[4] Furthermore, other conditions such as pseudoseizures and syncope may be confused with epileptic seizures.[4] Diagnosis should therefore be confirmed by a professional with expertise in epilepsy. Diagnostic imaging modalities, including MRI and CT, and an EEG are helpful to confirm diagnosis and clarify treatment.[4]

Treatment options for managing epilepsy in NZ

Epilepsy is mainly treated with antiepileptic drugs (AEDs). This pharmacological treatment approach endeavours to ensure freedom from seizures without interfering with normal cognitive function and development, and with minimal adverse effects.[2,13] Although AED monotherapy controls seizures in many patients, approximately 30% of patients may require treatment with multiple AEDs and some patients will continue to experience seizures despite such treatment.[14] In patients with severe refractory

epilepsy and established seizure-related disability it may be necessary to consider resective or palliative surgery.[14]

Pharmacological treatment options include a wide range of older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone and valproate), as well as the newer second-generation agents (levetiracetam, gabapentin, lacosamide, lamotrigine and topiramate).[14] In general, the efficacy of the newer AEDs, appears to be similar to that of the older AEDs.[14] However, the newer agents such as the broad-spectrum AED, levetiracetam, appear to offer improved tolerability, simpler titration and administration regimens, and a lower risk of interactions with other medications.[14] In fact, levetiracetam can be introduced at an effective starting dose of 1000 mg/day in adults without the slow titration usually required with add-on AEDs.[1]

About levetiracetam

In New Zealand, levetiracetam is currently approved for use in epileptic patients ≥6 years of age, as add-on therapy, in the treatment of partial-onset seizures with or without secondary generalisation.[1]

Levetiracetam is contraindicated in patients with a known hypersensitivity to levetiracetam or any of the inactive ingredients in the tablets.[1] In New Zealand, REX Medical Ltd's brand of levetiracetam [Everet] is fully subsidised by PHARMAC without the requirement for Special Authority approval.

Levetiracetam has a favourable tolerability profile and the majority of adverse events associated with its use appear to be mild-to-moderate.[1,14] Furthermore, the agent does not exhibit clinically significant interactions with other drugs and therapeutic drug monitoring is not required.[1,14] The most common side-effects are behavioural or mood changes, which can occur in up to 10% of patients.[1,14]

Pharmacokinetics

Levetiracetam, a pyrrolidone derivative, is chemically unrelated to other available AEDs and its mechanism of action is not yet fully understood.

It is known that the agent binds to a synaptic vesicle protein, SV2A, and modulates synaptic vesicle exocytosis, causing direct inhibition of presynaptic neurotransmitter release.[15,16] Levetiracetam also reduces the release of calcium from intraneuronal stores, partially inhibits the N-type calcium channel and opposes the activity of the negative allosteric modulators β-carbolines and zinc on GABA- and glycine-gated currents.[17]

Levetiracetam is a permeable and highly soluble compound with a linear pharmacokinetic profile.[1]

Pharmacological properties of levetiracetam[1,14]

Molecular mass	170.21 g/mol
Route of administration	Oral
Bioavailability	~100% – not influenced by food Peak plasma concentrations (C_{max}) are reached 1.3 hours after administration Steady state is achieved after twice-daily dosing for two days
Metabolism	Main metabolite is ucb L057 The metabolite is pharmacologically inactive
Elimination	Predominantly renal clearance – accounting for a mean of 95% of the dose 93% of the dose excreted within 48 hours Faecal excretion accounts for 0.3% of the dose
Plasma half-life	~7 ± 1 hours in adults ~6 ± 1.1 hours in epileptic children aged 5-12 years ~10 - 11 hours in the elderly due to decreased renal function in this population
Main toxicities	The most commonly reported adverse effects in adults are accidental injury, asthenia, somnolence, dizziness, infection and headache Behavioural or mood changes occur in up to 10% of patients In the paediatric population the most commonly reported undesirable effects are hostility, somnolence, emotional lability, nervousness, anorexia, agitation, headache and asthenia
Main drug interactions	No clinically significant interactions Therapeutic drug monitoring is not required

Dosage and administration[1]

Levetiracetam [Everet] tablets are film coated and available in 250 mg, 500 mg, 750 mg and 1000 mg doses, coloured as follows:
250 mg – light blue;
500 mg – yellow;
750 mg – light orange;
1000 mg – white.

Levetiracetam tablets must be taken whole, orally, swallowed with liquid. They may be taken with or without food.

The daily dose is to be administered in two equal dose amounts (i.e. 2 x 250 mg or 2 x 500 mg) and the tablets are not to be divided.

Adults and adolescents (aged 12-17 years) weighing ≥50 kg: therapeutic dose is 500 mg twice daily as adjunctive therapy (this dose may be started on the first day of treatment). The dose may be increased up to 1500 mg twice daily; maximum recommended daily dose is 3000 mg. Dose alterations can be made in 500 mg twice-daily increments or decrements every 2-4 weeks.

Elderly (≥ 65 years): Individuals with compromised renal function should have their dose adjusted. (see datasheet for dosage schedule based on renal function).

Children (aged 6-11 years) and adolescents (aged 12-17 years) weighing <50 kg: As adjunctive therapy the initial dose is 250 mg twice daily and this dose may be started on the first day of treatment. Depending on clinical response and tolerance, the dose may be increased to 750 mg twice daily (maximum recommended daily dose 1500 mg). Dose alterations can be made in 250 mg twice-daily increments or decrements every 2-4 weeks.

The physician should prescribe the most appropriate dose according to weight.

Infants and children <6 years of age: Everet tablets are not recommended for this age group.

Patients with renal impairment may require dose adaptation (see datasheet).

For patients with severe hepatic impairment and a creatinine clearance <60 mL/min/1.73 m^2, a 50% reduction of the daily maintenance dose is recommended. Patients with mild or moderate hepatic impairment do not require dose adjustment.

Evidence for the use of levetiracetam

Levetiracetam has proven efficacy as adjunctive therapy for controlling seizures in children and adults with partial-onset seizures with or without secondary generalisation.[14] Evidence, including that of a pivotal European multicentre, double-blind, randomised, placebo-controlled trial, showed that levetiracetam was efficacious and very well tolerated.[1,14,18] The study tested the efficacy and tolerability of levetiracetam 500 mg or 1000 mg twice daily as add-on therapy in 324 adult patients with uncontrolled simple or complex partial seizures, or both, with or without secondary generalisation.[18] At 12 weeks follow-up, levetiracetam 1000 mg/day and 2000 mg/day significantly ($p = 0.004$) decreased partial seizure frequency compared with placebo, with a reduction in seizure frequency of ≥ 50% occurring in 22.8%, 31.6% and 10.4% of patients, respectively.

Three other pivotal trials confirmed the efficacy of levetiracetam, with a median reduction from baseline in weekly seizure frequency across the four trials of 17.7-55.9% with levetiracetam 1000-3000 mg/day versus 6.1-13.7% with placebo; all $p \leq 0.001$ (**see Figure**).[14,18-21] The studies emphasise the fact that levetiracetam can be introduced at an effective starting dose (in this case 1000 mg/day) without the slow titration usually required in add-on AEDs.

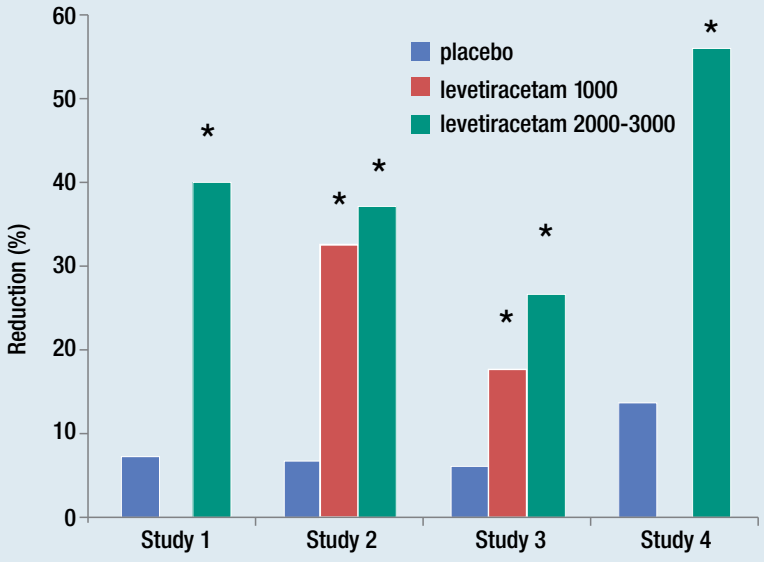


Figure. Reduction from baseline in number of refractory partial-onset seizures per week during adjunctive therapy with oral immediate-release levetiracetam (LEV) in adults (aged 16–70 years) in the modified intent-to-treat population of randomised, double-blind, placebo (PLA)-controlled, multicentre trials of twice-daily 1000 to 3000 mg LEV in addition to stable dosages of one or two other AEDs. (Study 1[19], Study 2[20], Study 3[18], Study 4[21]). * $p \leq 0.001$

The efficacy of levetiracetam was also evaluated in the SKATE trial, a phase IV, 16-week, open-label study of levetiracetam 1000-3000 mg/day as add-on therapy for refractory partial seizures in patients aged ≥16 years.[22] The findings in 1346 evaluated patients were that levetiracetam resulted in a median reduction from baseline in the frequency of all seizures of 50.2% (50.1% had a seizure frequency reduction of ≥50%) and 15.8% of patients were seizure free. Participants also exhibited a significant improvement in health-related quality of life with the Quality of Life in Epilepsy (QOLIE)-10-P total score increasing from 55.6 to 61.6 ($p < 0.001$).

A 2012 Cochrane review and pooled analysis of 11 trials (1861 participants including 296 children) investigating add-on levetiracetam for drug-resistant focal epilepsy, revealed that levetiracetam significantly reduced focal seizure frequency relative to placebo; RRs 2.49 (95% CI 1.78-3.50) at 1000 mg/day, 4.91 (95% CI 2.75-8.77) at 2000 mg/day and 2.59 (95% CI 2.01-3.33) at 3000 mg/day.[23] Across the 11 trials, the actual response rates for the different doses of levetiracetam were: 1000 mg 33%; 2000 mg 37%; 3000 mg 44%, compared with 13%, 8% and 18% with placebo, respectively.[23]

The KEEPER trial an open-label community-based study involving adjunctive levetiracetam 500-1500 mg twice-daily for partial-onset seizures in 1030 patients followed for 16 weeks, confirmed the efficacy of the agent, reporting that 57.9% of patients experienced at least a 50% reduction in the frequency of partial-onset seizures, 40.1% experienced at least a 75% reduction, and 20% demonstrated a 100% seizure reduction.[24] Furthermore, on the investigator-completed clinical impression rating, 74.3% of levetiracetam recipients were considered improved, with 37% showing marked improvement.

Comparator trials

While there is a distinct lack of active trials investigating the comparative efficacy and tolerability of levetiracetam against other AEDs, a small number of studies, audits and meta-analyses give some insight.

A 2005 meta-analysis of randomised placebo-controlled clinical trials of add-on therapy with levetiracetam, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate and zonisamide in patients with refractory partial epilepsy identified in the Cochrane Library found that levetiracetam was more effective in terms of responder rate than gabapentin (OR 2.64; 95% CI 1.51-4.63) and lamotrigine (OR 1.86; 95% CI 1.04-3.34) and equally well tolerated.[25] Furthermore, levetiracetam exhibited a significantly lower withdrawal rate than topiramate (OR 0.52; 95% CI 0.29-0.93) and oxcarbazepine (OR 0.55; 95% CI 0.33-0.92), with comparable efficacy.

In a subsequent review of over 500 long-term open-label studies of eight AEDs, levetiracetam exhibited the best efficacy profile (number of patients who achieve seizure freedom for 6 months) and was the best-tolerated AED.[26] Another systematic review and meta-analysis involving 43 trials using AEDs for refractory focal epilepsy in 6346 patients, found that among a wide range of AEDs, levetiracetam, sodium valproate and gabapentin exhibited the best balance of efficacy and tolerability, while a 2014 evaluation of data from prospective audits of five AEDs for focal epilepsy including levetiracetam, revealed a greater proportion of seizure-free patients with levetiracetam (23.5%), lacosamide (21.9%) and topiramate (20.7%) than with zonisamide (12.8%) and pregabalin (10.4%).[27,28]

Levetiracetam in children

A multicenter, randomised, placebo-controlled trial of levetiracetam 60 mg/kg/day in 198 children (aged 4 to 16 years) with treatment-resistant partial-onset seizures, found a significant reduction in partial-onset seizure frequency per week compared with placebo (26.8%; 95% CI 14.0%-37.6%, p = 0.0002).[29] 44.6% of levetiracetam recipients experienced a ≥50% reduction in partial seizure frequency per week compared with 19.6% receiving placebo (p = 0.0002). 6.9% of levetiracetam-treated patients were seizure-free during the entire 14-week double-blind treatment period, compared with 1.0% of placebo-treated patients.

In the 2012 Cochrane review and pooled analysis (discussed above) levetiracetam significantly reduced focal seizure frequency relative to placebo among 296 children; RR 1.91 (95% CI 1.38-2.63) at a dose of 60 mg/kg/day, with a response rate of 52% vs 25% with placebo.[23] The analysis showed children to be better responders than adults (52% vs 39%).

Since the Cochrane review, a number of subsequent studies have demonstrated similar findings, including a number of long-term studies which have confirmed that adjunctive therapy with levetiracetam for partial seizures in children is clinically efficacious.[30-33] In one such study, a 48-week open-label, multicenter, extension study assessing cognition, behaviour, tolerability, safety, and efficacy of adjunctive levetiracetam (20-100 mg/kg/day) in children aged 4 to 16 years (n = 103) with partial-onset seizures, levetiracetam provided good and sustained seizure control with a median percentage reduction from baseline in partial-onset seizure frequency/week during maintenance of 86.4%; 24.7% of patients had continuous seizure freedom from all seizure types for ≥40 weeks. Furthermore, these children exhibited long-term stability in cognitive functioning and improvement in emotional/behavioural functioning.[33]

Levetiracetam in the elderly

The efficacy of the ten most commonly prescribed AEDs between 2000 and 2005 (levetiracetam, lamotrigine, carbamazepine, gabapentin, oxcarbazepine, clobazam, phenytoin, topiramate, valproate sodium and zonisamide) was investigated in older patients (mean age 66 years; n = 417; 77.6% with localisation-related epilepsy) in a retrospective review.[34] Levetiracetam was found to have one of the highest 12-month retention and seizure-freedom rates (73% and 43%).

Supporting the above results, are the findings of a 1-year observational study in 491 elderly (≥65 years) patients receiving add-on levetiracetam for focal epilepsy.[35] In that study, seizure freedom rates were 42%, 57.7%, and 58% at 3, 6 and 12 months follow-up, respectively. More recently, a randomised, double-blind, multicentre comparison of controlled-released carbamazepine, levetiracetam and lamotrigine in 359 elderly patients (≥60 years) with new-onset focal epilepsy showed similar seizure freedom rates at weeks 30 and 58 across the agents; levetiracetam 48.4% and 42.6%, carbamazapine 39.2% and 33.3%, lamotrigine 48.7% and 38.5%, respectively.[36]

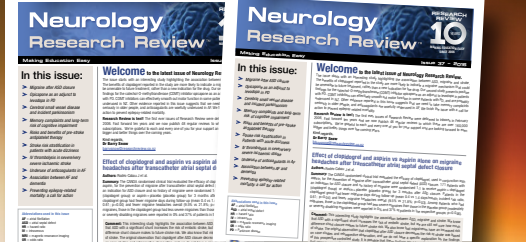
Tolerability

Treatment-emergent adverse events are commonly reported in add-on levetiracetam studies; however, most of these events are mild to moderate in severity.[14] Across the placebo-controlled pivotal trials in adults and children the overall rates of patients who experience at least one treatment-emergent adverse event are similar to those seen with placebo (53-89% vs 53-92%).[14]

In large, open-label, community-based, 16-week trials of levetiracetam for partial-onset seizures, the most frequently reported adverse events associated with levetiracetam were: somnolence (12.8% to 30.3%), dizziness (6.9% to 14.7%), fatigue (6% and 13.7%), asthenia (8.3%), headache (5.9% to 10.3%), sedation (6%) and nausea (3.8% and 5.6%).[14] Overall, 7.2-12.9% of patients discontinued the agent due to treatment-related adverse events.[14] It appears that psychiatric and behavioural adverse events including agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability and personality disorders occur in up to 10% of patients treated with levetiracetam.[14]

A recent meta-analysis of 25 studies involving 2832 participants has revealed that those receiving levetiracetam were significantly more likely than those receiving placebo to discontinue treatment (risk difference [RD] 0.03; 95% CI 0.01-0.05).[37] The adverse events associated with levetiracetam identified in the meta-analysis were; nasopharyngitis (RD 0.03; 95% CI 0.00-0.06); nervousness/irritability (RD 0.06; 95% CI 0.02-0.09), asthenia/fatigue (0.07; 95% CI 0.04-0.10), somnolence (RD 0.07; 95% CI 0.05-0.09) and dizziness (RD 0.04; 95% CI 0.02-0.06). The study authors concluded that levetiracetam has a good tolerability profile, characterised mainly by a sedative effect (somnolence, asthenia, fatigue), along with mild vestibulocerebellar manifestations characterised by dizziness, a weak increase in upper respiratory tract infections and minimal neuropsychiatric impairment (nervousness/irritability).

A number of comparative studies have found retention rates to be higher with levetiracetam than with other AEDs.[14,34,36,38]



Levetiracetam in pregnancy

Levetiracetam should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus.[1] Post-marketing data do not suggest a substantial increase in the risk of major congenital malformations or developmental delays, however, a teratogenic risk cannot be completely excluded.[1,14,39-41]

A Danish population-based cohort study published in JAMA in 2011, revealed no birth defects among 58 infants exposed to levetiracetam during the first trimester, while a systematic review of eight studies reporting on 1213 levetiracetam monotherapy- and polytherapy-exposed pregnant women during the first trimester found the risk of major fetal malformation to be within the population baseline risk of 1-3%.[39,41] This was the rate of major fetal malformations observed with levetiracetam monotherapy exposure in the first trimester in the 450 subjects identified in the North American AED Registry in which 11 (2.4%) such malformations occurred.[42] Data from the UK and Ireland epilepsy and pregnancy registers revealed 19 major congenital malformations among 367 patients receiving levetiracetam polytherapy; 5.56% (95% CI 3.54%-8.56%).[43] This rate varied by regimen, with lower rates when levetiracetam was given with lamotrigine (1.77%; 95% CI 0.49%-6.22%) than when given with valproate (6.90%; 95% CI 1.91%-21.96%) or carbamazepine (9.38%; 95% CI 4.37%-18.98%).

A UK study looking at the cognitive development of children (aged <24 months), revealed that those exposed *in utero* to levetiracetam ($n = 51$) did not significantly differ to control children representative of the general UK population in overall developmental ability, but exhibited significantly ($p < 0.001$) higher developmental scores when compared to children exposed to sodium valproate ($n = 44$).[40] For overall development quotient, those with levetiracetam exposure exhibited significantly ($p < 0.001$) higher scores than those exposed to sodium valproate. The broad-spectrum efficacy of levetiracetam as well as this early data suggesting there is no major risk of cognitive impairment, has led to increasing use of levetiracetam in pregnancy and in women of childbearing age. However, more data is needed to make a confident recommendation.

Expert concluding commentary

Levetiracetam has been widely used in New Zealand since 2010 and continues to be a very useful addition to the available anti-epileptic drugs. Follow-up long-term studies, as described above, show good efficacy and good tolerability, with little or no interaction with other AEDs and medications. Levetiracetam has the added advantage of being available in an intravenous formulation, although this is currently not registered in New Zealand.

Levetiracetam has proven to be efficacious in the treatment of partial-onset seizures. It is also a broad spectrum AED, which can be effective in the treatment of generalised epilepsies and myoclonus, although probably not as effective in absence seizures and genetic generalised epilepsy syndromes as sodium valproate. Randomised studies are currently underway to compare the efficacy and tolerability of levetiracetam with standard alternative agents (valproate, carbamazepine, lamotrigine), as first-line treatment in both focal onset and generalised epilepsies. Levetiracetam is particularly useful in older patients, and in patients with concomitant medical disorders, as it does not interact with other medications.

Ongoing observational studies of pregnancy registers have shown that levetiracetam used in monotherapy does not appear to be associated with a significant increase in major fetal abnormalities, and there have been no adverse effects on cognitive development in children exposed to levetiracetam. In polytherapy, the fetal outcome appears to be dependent on the coexistent drugs, especially valproate. As levetiracetam can be useful in the treatment of generalised epilepsies, levetiracetam is a useful alternative to valproate in women of childbearing age or considering pregnancy who have generalised epilepsy. During pregnancy, the renal clearance of levetiracetam increases significantly, although there is variability from patient to patient. The dose of levetiracetam usually needs to be increased during the second and third trimesters. In this circumstance, plasma drug levels can be very useful.

Although oral loading can be achieved, side effects are common, particularly mood-related change, agitation, depression and sedation.[14] Levetiracetam should, when possible, be titrated in reasonably slowly; this improves the tolerability of the drug in the longer term. Mood disorders can be a problematic side effect, both anxiety/agitation and depression, requiring withdrawal of drug therapy.[14] In the longer term, behavioural changes, depression and psychomotor retardation can occur, particularly in children.

Practice tips from the expert

Levetiracetam is a useful anticonvulsant agent in the treatment of both focal-onset seizures and generalised epilepsies. It is particularly useful in patients taking medication for other concomitant medical disorders due to the low rate of interaction. In the elderly and patients with renal disease, the dose needs to be lowered according to the degree of renal function.[1]

Due to the low incidence of major foetal malformation, and absence of deleterious effect on cognitive outcome, levetiracetam should be considered as an alternative to sodium valproate in teenagers and women of child-bearing age with generalised epilepsy syndromes, such as juvenile absence epilepsy, and juvenile myoclonic epilepsy. It can be used only for the duration of the pregnancy, or changed permanently.

Prescribers should be aware that mood disorders, particularly anxiety and depression, and sedation are significant side-effects, both early and late, and may necessitate withdrawal of treatment in up to 10% of patients. Although this drug can be initiated at 1000 mg per day, many patients do not tolerate this initial dose, and gradual titration using the 250 mg tablet size is recommended.

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