

Levetiracetam (Keppra[®]): A Review

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Less than ten years ago, patients and health-care providers were limited to choosing between six major antiepileptic drugs: phenobarbital, phenytoin, carbamazepine, valproic acid, primidone, and ethosuximide. Beginning in 1993, after a 15-year hiatus, a new generation of antiepileptic drugs began to win FDA approval.¹ Since then, eight new agents have reached the U.S. market: felbamate (Felbatol[®]), gabapentin (Neurontin[®]), lamotrigine (Lamictal[®]), levetiracetam (Keppra[®]), oxcarbazepine (Trileptal[®]), tiagabine (Gabitril[®]), topiramate (Topamax[®]), and zonisamide (Zonegran[®]).

Compared to the older generation agents (see Table I) the newer antiepileptic drugs are generally expected to have a more favorable safety profile and exhibit fewer drug interactions. One notable exception is felbamate, which earned a black box warning for aplastic anemia and hepatic failure.² As limited cumulative experience often precludes an accurate estimation of the true incidence of adverse effects of newly

marketed drugs, much remains to be learned about the comparative safety of these newer antiepileptic agents. Levetiracetam (Keppra[®]), one of the newest antiepileptic drugs, received FDA-approval in November 1999 and was added to the UWMC/HMC Drug Formulary in October 2000. This article will summarize the levetiracetam clinical experience to date, and briefly identify the key properties of the drug expected to translate into a comparatively low propensity to cause drug interactions.

Overview: Levetiracetam is FDA-approved as adjunctive therapy for partial-onset seizures in adults. Clinical studies assessing the safety and efficacy of levetiracetam in children are ongoing. Levetiracetam is available in 250, 500, and 750mg tablets. The recommended adult oral starting dose is 500mg twice daily. If higher doses are necessary to control seizure activity, the dose may be increased in 1g/day increments every two weeks, up to a maximum of 3g/day. Doses should be adjusted on the basis of renal function (see Table II) but do not have to be adjusted when hepatic dysfunction is present.³ Experience with doses greater than 3g/day is limited. An unintentional

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Table I: Adverse Events and Drug Interactions Associated with Older Antiepileptic Drugs

Agent	Major Adverse Events	Drug Interactions
Carbamazepine	aplastic anemia, agranulocytosis, Stevens-Johnson syndrome	many
Ethosuximide	mental slowness, mood changes, Stevens-Johnson syndrome	phenytoin, primidone
Phenobarbital	megaloblastic anemia, psychiatric disturbances, Stevens-Johnson syndrome	many
Phenytoin	gingival hyperplasia, hyperglycemia, Stevens-Johnson syndrome	many
Primidone	megaloblastic anemia, mood changes	carbamazepine, phenytoin, isoniazid
Valproic Acid	hepatotoxicity, pancreatitis, Stevens-Johnson syndrome	many

A University of Washington / Harborview Medical Center Drug Information Center publication
 Distributed monthly by authority of the Pharmacy and Therapeutics Committee
 Editor: Nelda A. Murri, Pharm.D. (206) 598-6612 – Asst. Editor: Elizabeth Rudy, D.V.M., R.Ph.
 Department of Pharmacy Services / School of Pharmacy

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Approximately 5 out of every 1,000 people suffer from epilepsy. 30-40% of patients with epilepsy have seizures that are inadequately controlled by their current drug regimen.¹⁵

Key Characteristics of Levetiracetam That Make It an Attractive Option for Treating Partial-Onset Seizures

- Wide therapeutic window
- Good bioavailability
- Linear pharmacokinetics
- Minimal drug interactions
- Rapid time to steady-state

Levetiracetam is unlikely to interact with drugs metabolized by CYP450 enzymes, and it is unlikely to competitively displace highly protein-bound drugs such as warfarin.

CNS side effects are the most commonly reported adverse effects of levetiracetam. Leukopenia, neutropenia, pancytopenia, and thrombocytopenia have also been reported clinically.

overdose of 6g/day (36g total over 6 days) is the highest known dose of levetiracetam.⁴ In this case, somnolence was the only adverse effect noted. To date, levetiracetam has been used by approximately 120,000 patients in the U.S.⁵ Significant randomized controlled published clinical trials are summarized in Table III.

Table II: Levetiracetam Dosing in Patients with Impaired Renal Function

Creatinine Clearance (mL/min)	Dose	Frequency
> 80	500 - 1500mg	q 12h
50 - 80	500 - 1000mg	q 12h
30 - 50	250 - 750mg	q 12h
< 30	250 - 500mg	q 12h
ESRD on dialysis	500 - 1000mg	q 24h (250 - 500mg supplemental dose after dialysis is recommended)

Drug Interactions: Drug interaction considerations are important for patients with

epilepsy for two reasons. First, most patients will require lifelong therapy with one or more antiepileptic drugs. Second, many will require episodic or chronic drug treatment for comorbid conditions. Without careful patient management, the initiation or discontinuation of drugs prescribed in combination with antiepileptic agents can lead to drug interactions that in turn may result in either excessive toxicity or breakthrough seizures.¹ Given that there are three main mechanisms known to be associated with most clinically important antiepileptic drug interactions (alteration of cytochrome P450 (CYP450) hepatic metabolism, protein-binding displacement, and physicochemical interference with absorption),⁶ the pharmacodynamic properties of levetiracetam suggest that minimal clinically important drug interactions are to be expected with this agent. Levetiracetam is neither metabolized by CYP450 liver enzymes, nor is it highly protein bound (protein binding <10%). Thus, different from most other antiepileptic drugs, levetiracetam is unlikely to interact with drugs metabolized by CYP450 enzymes, and it is unlikely to competitively displace highly protein-bound drugs such as warfarin.⁷ In clinical studies, levetiracetam did not appear to interact with carbamazepine, digoxin, gabapentin, lamotrigine, oral contraceptives, phenobarbital, primidone, valproic acid, or warfarin.^{7,8} One author noted a 27-52% increase in serum phenytoin levels in four of six patients studied; however, three larger studies failed to detect a significant interaction between levetiracetam and phenytoin.^{9,10} Nevertheless, because of the contradictory findings, practitioners are advised to check serum phenytoin levels within one week of initiating therapy with either drug, and at any time that signs suggestive of drug toxicity appear.³

Adverse Effects: Analysis of pooled data generated prior to FDA approval revealed that when combined with other antiepileptic agents, the most commonly recorded adverse effects with levetiracetam were somnolence (15%), asthenia (15%), behavioral symptoms such as agitation, anger, hostility, anxiety, apathy, irritability, and depression (13.3%), and dizziness (9%).^{4,5} Less common CNS side effects were psychosis (0.7%) and suicidal ideations (0.5%).⁸ Overall, 15% of patients experienced side effects serious enough to require dosage reduction or discontinuation of levetiracetam add-on therapy.⁴ While more prevalent during the first four weeks of therapy, if debilitating to the patient, adverse CNS effects may require backing down on the daily dose or slowing upward dosage titration.³

Hematologic side effects of levetiracetam are also noteworthy. Compared to controls, small but statistically significant decreases in RBCs ($0.03 \times 10^6/\text{mm}^2$), hemoglobin (0.09g/dL), and hematocrit (0.38%), as well as decreases in neutrophils and WBCs, were

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Table III: Summary of Randomized, Double-Blind, Placebo-Controlled, Multi-Centered Levetiracetam Trials

Study Objective (Author)	Inclusion Criteria	Exclusion Criteria	Groups	N	Primary Efficacy Result	Withdrawals Due to Adverse Events	Rate of Adverse Events	Comments
Evaluation of levetiracetam as adjunctive therapy in refractory partial seizures (Cereghino ¹¹)	Age 16-70 years; Uncontrolled partial seizures for ≥ 2 yrs; ≥ 12 partial seizures within 12 wks before study; ≥ 2 partial seizures/month during baseline period; ≥ 2 antiepileptics simultaneously or consecutively	Women of childbearing age on < 2 simultaneous methods of birth control or with a positive serum pregnancy test; Concomitant conditions or chronic progressive neurologic disease; Participation in other drug trial within 4 wks; History of drug or alcohol abuse; Renal or hepatic insufficiency	control	95	—	5.3%	88.4%	Most common concomitant antiepileptics: carbamazepine (55.7%), phenytoin (34%), gabapentin (27.7%), valproic acid (26%); Most common reason for withdrawal: somnolence.
			levetiracetam 0.5g BID	98	20.9% reduction in partial seizure frequency vs. control (p<0.001)	6.1%	88.8%	
			levetiracetam 1.5g BID	101	27.7% reduction in partial seizure frequency vs. control (p<0.001)	6.9%	89.1%	
Evaluation of levetiracetam as adjunctive therapy in refractory partial seizures with or w/o secondary generalization (Shorvon ¹²)	Age 16-65 years; Seizures persisting for previous 2 yrs or more despite 1-2 antiepileptics; Stable dose(s) of antiepileptics for at least 4 wks before & throughout study; ≥ 4 partial seizures/month during baseline period	Women of childbearing age not using contraception or not surgically sterilized; Renal insufficiency; Progressive neurologic disorders; Serious psychiatric disorders; Abnormal labs at baseline; Substance abuse; Questionable compliance	control	112	—	5.4%	73.2%	Most common concomitant antiepileptics: carbamazepine (72%), phenytoin (22%), valproic acid (21%); Most common side effects: somnolence, asthenia, headache.
			levetiracetam 0.5g BID	106	16.4% reduction in partial seizure frequency vs. control (p=0.006)	7.5%	70.8%	
			levetiracetam 1g BID	106	17.7% reduction in partial seizure frequency vs. control (p=0.003)	14.2%	75.5%	
Conversion from adjunctive therapy to monotherapy in patients with refractory partial seizures (Ben-Menachem ¹³)	Age 16-70 years; Partial seizures for ≥ 1 yr before study; ≥ 2 complex partial seizures/month during baseline period while on 1 antiepileptic	Women of childbearing age not using contraception or not surgically sterilized; History of status epilepticus, seizure clusters, drug/alcohol abuse, progressive cerebral disease, cerebrovascular accident, cardiovascular disease; Concurrent digitalis, coumarins, barbiturates, benzodiazepines, neuroleptics, antidepressants, anxiolytics, tranquilizers, anticholinergics, psychostimulants, or analgesics; Disturbance of hemostasis; IDDM; Unstable hyperthyroidism; Renal or hepatic impairment; Poor compliance; Psychiatric disorders; Participation in prior clinical trials	placebo	105	9.5% had good seizure control for 12 wks (completed 12 wk monotherapy phase)	9.5%	53% (Add-on phase only)	Most common side effects: asthenia, infection (mostly common colds), somnolence, headache; Levetiracetam monotherapy: 73.8% (p=0.037) median reduction in seizure frequency vs. baseline, but 0.04 median increase in seizure frequency vs. add-on phase.
			levetiracetam 1.5g BID	181	19.9% had good seizure control for 12 wks (p=0.029) (completed 12 wk monotherapy phase)	10.5%	55% (Add-on phase only)	
Evaluation of levetiracetam as adjunctive therapy without titration in refractory epilepsy of any type (Betts ¹⁴)	Age 16-70 years; Refractory epilepsy of any seizure type; Stable dose of ≤ 3 antiepileptics for ≥ 3 months prior to study; ≥ 4 seizures in the 24 wks prior to study	Women of childbearing age not using contraception; History of allergy, alcohol, or drug abuse; Serious medical conditions; Psychotic conditions; Problems with absorption, metabolism, or elimination of drugs; Renal or hepatic insufficiency	control	39	5/31 patients (16.1%) had $\geq 50\%$ reduction in seizure frequency after 24 weeks	15.4%	84.6%	Most common concomitant antiepileptics: carbamazepine (N=69), valproic acid (N=38), phenytoin (N=37), phenobarbitone (N=25); Most common reason for withdrawal: somnolence.
			levetiracetam 1g BID	42	13/27 patients (48.1%) had $\geq 50\%$ reduction in seizure frequency after 24 weeks (p=0.01 vs. control)	26.2%	83.3%	
			levetiracetam 2g BID	38	8/28 patients (28.6%) had $\geq 50\%$ reduction in seizure frequency after 24 weeks	13.2%	84.2%	
Evaluation of levetiracetam as adjunctive therapy in refractory partial seizures (Boon ¹⁵)	Age 16-65 years; Strictly/predominately partial seizures incompletely controlled on 1-2 antiepileptics during 2 yrs prior to study; Stable drug dose(s) for ≥ 4 wks; ≥ 4 partial seizures/month during baseline period	Women of childbearing age not on contraception or not surgically sterilized; Concomitant medical conditions; Chronic progressive neurologic disease; History of drug/alcohol abuse; Renal or hepatic impairment	control	200	—	8%	72%	Most common concomitant antiepileptics: carbamazepine (72%), phenytoin (22%), valproic acid (21%); Most common adverse effects: headache, asthenia, dizziness, infection, pharyngitis, somnolence, pain.
			levetiracetam 0.5g BID	200	16.9% reduction in partial seizure frequency vs. control (p<0.001)	7%	67.5%	
			levetiracetam 1g BID	202	18.5% reduction in partial seizure frequency vs. control (p<0.001)	12.9%	75.5%	

Levetiracetam (Keppra[®]): A Review (continued)

Practitioners are advised to be alert for signs of hematologic abnormalities and to periodically monitor blood cell counts in patients receiving levetiracetam.

The newer antiepileptics are more expensive than older antiepileptic drugs.

Note: The editor gratefully acknowledges the assistance of Bridget A. Haupt, Pharm.D., and John W. Miller, M.D., in reviewing this article.

References available upon request.

observed in pre-marketing clinical trials.⁸ More recently, uncontrolled clinical reports of leukopenia, neutropenia, pancytopenia, and thrombocytopenia have surfaced.⁵ In light of these cases, practitioners are advised to be alert for signs of hematologic abnormalities and to periodically monitor blood cell counts in patients receiving levetiracetam.

Conclusion: Currently, carbamazepine and phenytoin are considered first-line agents for partial seizures with or without secondary generalization, and valproic acid is considered second-line.¹⁰ Newer agents including levetiracetam, gabapentin, lamotrigine, tiagabine, and topiramate are all FDA-approved as adjunctive therapy.¹⁰ As no head-to-head clinical trials of levetiracetam against other antiepileptics have been performed, it is not currently possible to rank order the comparative safety and efficacy of these agents. Compared to the other newer antiepileptics, levetiracetam appears to be a relatively safe option because of its low risk of drug interactions. The comparative costs of the newer UWMC/HMC Formulary antiepileptic agents are shown in Table IV.

Table IV: UWMC/HMC Patient Cost for Levetiracetam vs. Alternative New Antiepileptic Drugs for Adjunctive Therapy of Partial-Onset Seizures

AED	Quantity	Cost per Month
Levetiracetam	500mg #60	\$117.60
	750mg #60	\$171.30
Gabapentin	300mg #90	\$111.75
	600mg #90	\$207.25
Lamotrigine	100mg #60	\$131.90
	200mg #60	\$144.85
Oxcarbazepine	600mg #60	\$217.15
Tiagabine	16mg #60	\$93.55
Topiramate	200mg #60	\$216.75
Zonisamide	100mg #60	\$103.60
	100mg #120	\$203.20

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VOL. 31, NO. 6

**Supplement:
Contemporary Issues
in Drug Therapy**



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