*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# Levetiracetam

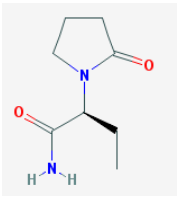
**Evidence Summary**

Cognitive benefits with levetiracetam have been observed in people with epilepsy, MCI, and brain injury. Side effects include drowsiness, fatigue, irritability, and increased infections.

**Neuroprotective Benefit:** Some cognitive benefits with levetiracetam have been observed in people with epilepsy, MCI, AD with epilepsy, brain tumor, and traumatic brain injury. Benefits may depend on the presence of epileptiform activity.

**Aging and related health concerns:** Although a few case studies suggested relief from peripheral neuropathy, meta-analyses have failed to find significant benefits.

**Safety:** Levetiracetam is well-tolerated but is associated with somnolence, fatigue, dizziness, irritability, and infections. There are major drug interactions with pain killers and caffeine. Levetiracetam may also increase the risk of rhabdomyolysis.

| | | |
|---|---|---|
| **Availability**: Rx | **Dose**: 1,000-3,000 mg/day, orally in epilepsy patients; 100-300 mg/day, orally, have been tested in people with mild cognitive impairment | **Chemical formula:** $C_8H_{14}N_2O_2$<br>**MW**: 170.212<br>  |
| **Half life**: 6-8 hours | **BBB**: penetrant | |
| **Clinical trials**: The largest meta-analysis included 26 RCTs with 2,832 patients. | **Observational studies**: Most studies have been in epilepsy patients. One longitudinal study included 109 subjects, 40 on levetiracetam. | |

**What is it?**

Levetiracetam (marketed as Keppra XR, Keppra, Spritam, Roweepra) is an atypical anti-epileptic prescription medication approved in 1999 as a second-generation drug. It is most often used as an add-on therapy in the treatment of epilepsy. The precise mechanism through which levetiracetam exerts its effects is unknown. Functionally, it selectively prevents hypersynchronization of epileptiform burst firing and propagation of seizure activity (DrugBank). Molecularly, levetiracetam has high affinity for the presynaptic membrane protein SV2A, which is widely expressed throughout the brain including high levels in the hippocampus [1]. Levetiracetam acts as an agonist at SV2A, which in turn inhibits neurotransmitter release (DrugBank). Based on the strong linear correlation between affinity to SV2A and the ability to protect against seizures in a mouse model of audiogenic seizure, it appears that action on SV2A is one of levetiracetam's main mechanisms of action, though other targets have also been proposed (discussed below).

Evidence from preclinical models and human patients suggest that neuronal circuits become hyperactive prior to the development of Alzheimer's disease [2; 3]. Studies suggest that treatment with low-dose, but not the higher doses used for epilepsy, attenuates neural overactivity [4; 5; 6]. Based on these findings, low-dose levetiracetam has been explored in people with early phases of Alzheimer's disease, including mild cognitive impairment.

**Neuroprotective Benefit:** Some cognitive benefits with levetiracetam have been observed in people with epilepsy, MCI, AD with epilepsy, brain tumor, and traumatic brain injury. Benefits may depend on the presence of epileptiform activity.

*Types of evidence:*

- 8 meta-analyses in various patient populations
- 1 double-blind randomized controlled trial in people with mild cognitive impairment
- 2 double-blind randomized controlled crossover studies in Alzheimer's patients
- 9 controlled clinical trials in various patient populations
- 5 open-label studies
- 1 case study in Lewy Body Dementia
- 3 fMRI studies
- 1 observational study in glioma patients
- Numerous review articles
- Numerous laboratory studies

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

Numerous studies have been carried out in humans, though most have been in patients with epilepsy/seizures.

In a 2024 meta-analysis of 16 randomized controlled trials including a total of 545 participants in various study populations (focal seizures, history of drug abuse, amnestic mild cognitive impairment, alcohol use disorder, Alzheimer's disease, schizophrenia, mania, healthy people, elderly people, and people with asthma on corticosteroids), levetiracetam treatment (dose ranging from 250 to 2,000 mg daily or based on body weight) was associated with improved executive function when compared to placebo (Hedges' g=-0.390; 95% CI, -0.609 to -0.172; p<0.001) [7]. There were no significant differences found in processing speed, working memory, verbal memory and learning, visuospatial memory and learning, or language between levetiracetam treatment and placebo. Subgroup analysis in patients without epilepsy showed that levetiracetam treatment outperformed placebo in executive function (Hedges' g=-0.419, 95% CI, -0.647 to -0.191; p<0.001) and visuospatial memory and learning domains (Hedges' g=-0.297, 95% CI, -0.530 to -0.065; p=0.012). Low-dose levetiracetam (below 500 mg or 7.5 mg/kg, daily) was also associated with improved executive function (Hedges' g=-0.544; 95% CI, -1.085 to -0.003; p=0.049) and visuospatial memory and learning (Hedges' g=−0.253; 95% CI, −0.493 to −0.014; p=0.038). The Stroop

test results were better with levetiracetam treatment compared to placebo (Hedges' g=−0.355; 95% CI, −0.569 to −0.141; p=0.001), but no significant levetiracetam effect was observed in the Trail Making Test B or the Wisconsin card sorting test results. Potential publication bias was observed for the executive function domain. Also, duration of treatment varied from acute treatment in 4 studies and durations varying from 1 week to 24 weeks in the remaining 12 studies. Due to the diverse study populations, variable treatment durations, and potential publication bias, further studies are needed to draw conclusions.

*Epilepsy patients*: BENEFIT.
In a 2012 Cochrane meta-analysis of 11 randomized controlled trials (total of 1,861 subjects) in drug-resistant focal epilepsy patients, add-on levetiracetam treatment (1,000-4,000 mg/day in adults, 60 mg/kg/day in children) for 12 -24 weeks significantly reduced focal seizure frequency and had a positive effect on cognition and some aspects of quality of life in adults [8]. However, in children, levetiracetam did not appear to alter cognitive functions.

In an open-label trial of 55 drug-naïve epilepsy patients, levetiracetam monotherapy for 1 year significantly improved verbal and visual attention, psychomotor speed, mental flexibility, executive function, verbal fluency and word generation [9]. There were 25 measures of cognitive functions plus 2 measures of mood, of which 14 cognitive measures had p-values under 0.05 (difference between pre-LEV and post-LEV). None of the neuropsychological domains showed significant decline. No changes in mood were found.

A smaller open-label trial of 27 patients with drug-resistant epilepsy also reported that levetiracetam add-on treatment (500 mg/day initially, then increased up to 1,000-3,000 mg/day) for 1 year significantly improved measurements of prospective memory, working memory, motor functions, verbal fluency, attention, and quality of life [10]. As in the study above, the study was small and there was no control group.

In a retrospective analysis of 91 adults with temporal lobe epilepsy, treatment with levetiracetam and oxcarbazepine (another anti-seizure medication) for 3 months resulted in significantly improved seizure control and memory function (measured by the Clinical Memory Scale and Wechsler Adult Intelligence Scale-Revised in China), and these improvements were superior to the control group receiving levetiracetam alone [11]. The group receiving both levetiracetam and oxcarbazepine had significantly higher scores in free recall, associative learning, and directed recall ($p<0.001$ for all) compared to the group receiving levetiracetam alone. Treatment with the combination of levetiracetam and

oxcarbazepine also resulted in better anxiety and depression scales (HAMA and HAMD, respectively; p<0.001 for both) compared to levetiracetam alone. The initial dose of levetiracetam was 500 mg per dose, orally, with increments of 500 mg per day, and the treatment was maintained at the minimum effective dose, not exceeding 1500 mg per dose. The initial dose for oxcarbazepine was 8-10 mg/(kg/d), twice a day, and subsequently increased by 5-10 mg/(kg/d) per week, up to a maximum of 45 mg/(kg/d).

In a 2019 meta-analysis and systematic review of 18 randomized controlled trials evaluating 12 anti-epilepsy medications in elderly epilepsy patients, levetiracetam was associated with a higher probability of seizure freedom when compared to lamotrigine, but not clearly when compared to carbamazepine [12]. Many of the drugs included in the meta-analysis only had single studies (brivaracetam, gabapentin, lacosamide, perampanel, and topiramate). More evidence of newer anti-epilepsy medications are needed, including how they compare with prior generation medications.

*Healthy adults*: UNCLEAR.
In a small placebo-controlled clinical study of 12 healthy adults, a single dose of levetiracetam (500 mg) significantly improved visual attention as measured by the Trail Making Test Part A [13]. No differences were seen in other neuropsychological parameters such as working memory, inhibitory control of attention, planning, and decision-making. It is not possible to extrapolate these findings to potential benefits with chronic treatment.

*Healthy elderly*: UNCLEAR.
In a double-blind randomized controlled cross-over trial in 20 healthy elderly (65-80 years old), 6 weeks of levetiracetam treatment (250 mg twice daily for 2 weeks, then increased to 500 mg twice daily, then tapered back to 250 mg twice daily) significantly improved visual memory (MCG Complex Figure Recall) and 2 attention tests (Trail Making Test Part A and Stroop Interference) compared to placebo [14]. However, there were 29 other tests that failed to show a difference compared to placebo, so it is unclear whether the significant improvements occurred by chance. There was a trend for greater irritability and fatigue during the levetiracetam phase. Effect-size changes were generally small (Cohen's d < 0.5) and no effects were seen for psychomotor speed or language.

*Amnestic MCI patients*: UNCLEAR.
People with amnestic mild cognitive impairment (aMCI) have hyperactivity in the hippocampus (dentate gyrus/CA3 region) during episodic memory tasks [4]. In a functional MRI study that included 54 aMCI patients, this hyperactivity was significantly greater compared to an aged control group without aMCI (n=17). When aMCI patients were treated with 62.5 or 125 mg twice daily doses of levetiracetam, there

was a significant improvement in memory task performance (**Table 1** pasted below) including improved accuracy and reduced errors, while normalizing fMRI activation in the hippocampus. Higher dosing at 250 mg twice daily had no significant benefit on fMRI activation and less pronounced cognitive benefits, suggesting that there is an optimal dose for optimal performance.

In an older study from the same group, a randomized controlled trial in 17 aMCI reported that levetiracetam treatment (125 mg twice daily) for 2 weeks reduced hippocampal activation to a level that did not differ from the control group (17 healthy older adults) [5]. Compared to aMCI memory performance under placebo, performance in the three-choice memory task was significantly improved with levetiracetam.

In a double-blind randomized placebo-controlled trial (named HOPE4MCI study) of 164 people with mild cognitive impairment due to Alzheimer's disease, extended-release low-dose levetiracetam (AGB101; 220 mg, orally every morning, once daily) for 18 months did not significantly affect the cognitive/functional composite score, which was the primary endpoint (CDR-SB; mean change was 1.12, 95% CI, 0.66 to 1.69 for the AGB101 arm and 1.22, 95% CI, 0.75 to 1.78 for the placebo arm) [15]. The AGB101 group had an 8% less worsening in the CDR-SB score compared to the placebo group, but this difference was not statistically significant. There were also no statistically significant differences between the AGB101 and placebo arms in secondary clinical measures (FAQ, MMSE, and BPS-O). The clinical trial was originally planned to be powered to serve as a phase 3 registration trial with a sample size of 830 participants. However, the planned sample size was reduced to 160 due to funding limitations and the need to obtain initial clinical efficacy data. The baseline characteristics were similar between AGB101 and placebo arms, but the number and percent of APOE4 carriers was higher (n=54, 68%) in the AGB101 arm compared to the placebo arm (n=45, 55%). In a prespecified analysis, the difference between AGB101 and placebo arms in CDR-SB was -0.45 favoring AGB101 (95% CI, -1.43 to 0.53) for APOE4 noncarriers and -0.10 (95% CI, -0.92 to 0.72) for APOE4 carriers. Numerically, this corresponds to 40% less change in the CDR-SB after 18 months of AGB101 treatment compared to placebo in APOE4 noncarriers; however, this difference was not statistically significant. Among APOE4 carriers, there was essentially no numeric or statistical difference on any primary or secondary measure between AGB101 and placebo arms. To test the hypothesis that AGB101 affects APOE4 noncarriers and APOE4 carriers differently, a study with significantly more participants is needed.

*Elderly with cognitive impairment and seizures*: BENEFIT.
In an open-label prospective phase 4 study in 24 elderly patients with cognitive impairment and seizures, levetiracetam treatment (250 mg twice daily at first, then increased to final dose between 250

and 1500 mg twice daily) for 12 weeks significantly improved cognitive functions as measured by Mini Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) [16]. MMSE scores improved by an average of 2.2 points after 12 weeks. The expected decline over 3 months in this population was 1 point. Improvement for the delayed recall portion of MMSE was 0.6 points (on 3-word recall). ADAS-Cog scores improved by an average of 4.3 points. No significant changes were seen in behavioral or functional measures. There was little change in caregiver-reported behavior and function and no significant change in the activities of daily living (ADL) scale.

*Children with autism and subclinical epilepsy*: BENEFIT.
In a prospective randomized controlled trial in 70 children with autism and subclinical epileptiform discharges, levetiracetam treatment (60 mg/kg/day) combined with educational training for 6 months normalized electroencephalographic measures while significantly improving behavioral and cognitive functions as measured by autism scores (CARS and ABC) [17]. The differences were significant compared to the control group which received educational training but no medications.

*Brain tumor patients*: POTENTIAL BENEFIT.
In a cohort study of 117 patients with high-grade glioma, those who were on levetiracetam performed better on verbal memory tests than patients not on an anti-epileptic drug [18]. No differences were found for other cognitive functions, such as attention, executive function, working memory, psychomotor function, and information processing speed.

*Brain injury patients*: PREVENTS POST-TRAUMATIC EPILEPSY
Seizures are common after traumatic brain injury and are associated with longer ICU stay and higher disability burden. In a 2022 network meta-analysis of randomized and non-randomized controlled trials, various anti-seizure medications were evaluated for the prevention of seizures in brain injury patients [19]. All tested anti-seizure medications (phenytoin, phenytoin + phenobarbital, levetiracetam, phenytoin + levetiracetam, lacosamide) except for valproate significantly reduced the rate of early post-traumatic epilepsy in traumatic brain injury patients compared with the placebo. Levetiracetam treatment prevented both early and late post-traumatic epilepsy. Although levetiracetam treatment did not reduce the length of hospital stay, it significantly reduced the length of ICU stay. Of the anti-seizure medications studied in this network meta-analysis, the authors speculated that levetiracetam is the best treatment option for traumatic brain injury patients. However, further high quality clinical trials are needed to confirm these findings.

In a 2024 meta-analysis and systematic review of 10 randomized controlled trials testing various anti-seizure medications in adults with traumatic brain injury, levetiracetam (RR=0.20; 95% CI, 0.07 to 0.60) and phenytoin (RR=0.28; 95% CI, 0.13-0.57) were associated with lower risk of early seizures compared to placebo [20]. The evidence is uncertain for the effects of other anti-seizure medications on the risk of early seizures, as well as effects of any anti-seizure medication on the risk of late seizures or long-term outcomes such as all-cause mortality.

***Human research to suggest benefits to patients with dementia***:

*Alzheimer's patients*: UNCLEAR.
In patients with Alzheimer's disease, interictal epileptiform discharges are common and are associated with a more rapid rate of disease progression [21]. Silent seizures and interictal epileptiform discharges, collectively termed "subclinical epileptiform activity", has a prevalence between 22-54% in people with Alzheimer's disease [22].

In a double-blind controlled feasibility study in mild Alzheimer's patients (MMSE scores between 20-29), a single dose of levetiracetam (2.5 or 7.5 mg/kg, i.v.) did not alter cognitive performance [23]. The pattern of EEG data (decreased coherence in the lower frequency bands and increased coherence in the higher frequency bands) suggested a beneficial effect of levetiracetam in these patients, though at the time of publication, only 9 patients had been enrolled. Larger longitudinal studies and studies with healthy age-matched controls are needed to determine whether this represents a relative normalization of EEG patterns, whether it is unique to Alzheimer's as compared to normal aging, and whether longer term administration is associated with a beneficial clinical effect.

In a double-blind randomized controlled crossover phase 2a study (LEV-AD study) of 13 Alzheimer's patients without epilepsy (and 9 patients with epileptiform activity), levetiracetam treatment did not significantly improve NIH-EXAMINER composite score or secondary measures [24]. However, in patients with early-onset Alzheimer's disease (n=20; symptom onset before 65 years old), levetiracetam treatment improved Stroop interference naming subscale (net improvement, 4.0 points; 95% CI, 0.0-7.9 points; p=0.049), but not other cognitive measures. Because of the small sample size and lack of correction for multiple comparisons in the exploratory analyses, false positive results and subgroup confounders cannot be ruled out.

In a double-blind randomized controlled crossover proof of concept study (ILiAD study) of 8 mild to moderate Alzheimer's disease patients, levetiracetam treatment for 12 weeks did not significantly

benefit memory (measured by the Oxford Memory Task), mood (measured by NPI), or quality of life (measured by QoL, EQ-5D, DSRS) compared to placebo, though the very small sample size precludes making any conclusions [25]. The study had originally planned to recruit 30 participants to the study, but recruitment was limited due to restrictions from the COVID-19 pandemic. The levetiracetam dose was up-titrated to 500 mg, orally twice daily for 4 weeks, then maintained on this dose for 4 weeks, then down-titrated to 0 during the following 4 weeks. The "What was where" Oxford Memory Task was chosen as an outcome based on its sensitivity to early signs of working memory deficits in people with hippocampal dysfunction, including people with Alzheimer's disease [26]. However, this test required in-person assessment, which was not possible throughout the study due to the COVID pandemic, and therefore, data collection was interrupted at different stages of enrollment [25]. Only 2 subjects per arm had data from 2 timepoints per arm. (Since the study, the investigators developed a fully remote version of the "What was where?" Oxford Memory task, which is now available at https://oxfordcognition.org/. This computerized cognitive assessment can be performed remotely or in-person.) The MMSE cognitive testing was also administered only at baseline due to the COVID pandemic.

*Alzheimer's patients with epilepsy*: BENEFIT.
A 2021 Cochrane report examining anti-seizure medications for epilepsy in Alzheimer's patients only found 1 randomized controlled trial including 95 Alzheimer's patients with epilepsy [27; 28]. In this trial, patients were randomly assigned an antiepileptic drug as monotherapy: 38 were administered levetiracetam, 28 were administered phenobarbital, and 29 were administered lamotrigine. This study comprised a 4-week dose adjustment period (titrated to an effective dose) followed by a 12-month dose evaluation period. The mean daily dose of levetiracetam was 956 mg (range, 500 to 2000 mg/day), the mean daily dose of phenobarbital was 90 mg/day (range, 50 to 100 mg/day), and the mean daily dose of lamotrigine was 57.5 mg/day (range, 25 to 100 mg/day). All participants had concomitant cholinesterase inhibitor therapy for Alzheimer's disease. No significant differences between the treatment arms were observed for seizure freedom, which was the primary outcome. Levetiracetam treatment (started at 500 mg/day, then increased weekly by 500 mg) for 12 months improved attention and oral fluency. At 12 months in the levetiracetam group, 27/38 (71%) were responders, 11 of whom (29%) had become seizure-free and 16/38 had a greater than 50% reduction in seizure frequency. MMSE scores in the levetiracetam group improved by a mean of 0.23 points compared to baseline; similar improvement was seen in ADAS-cog scores (-0.23 points). The phenobarbital group showed significant worsening of cognitive performance, and the lamotrigine group showed slight declines in MMSE and ADAS-Cog scores. There was no placebo control—the control group had Alzheimer's without epilepsy.

In a double-blind randomized controlled crossover phase 2a study (LEV-AD study) of 9 Alzheimer's patients with epileptiform activity (and 18 patients without epileptiform activity), levetiracetam treatment improved executive function (measured by Stroop interference naming subscale; net improvement vs placebo, 7.4 points; 95% CI, 0.2-14.7 points; p=0.046) and spatial memory (measured by the virtual route learning test; t=2.36; p=0.02) [24]. Most patients with epileptiform activity had improved scores on the NIH-EXAMINER (6 of 8 patients) and the ADAS-Cog (7 of 9 patients) with levetiracetam treatment, although the p-values for group comparisons were not significant. Because of the small sample size and lack of correction for multiple comparisons in the exploratory analyses, false positive results and subgroup confounders cannot be ruled out.

*Dementia with manic behavior*: UNKNOWN.
In an open-label pilot trail of 19 geriatric patients with dementia and manic behavior, levetiracetam treatment (average of 592 mg daily) for ~12 days significantly improved mania scores but the treatment duration was too short to expect any changes in cognitive functions [29].

*Lewy body dementia*: UNKNOWN.
It is not known whether levetiracetam has cognitive benefits in people with Lewy body dementia. There was a case report of a man with Lewy body dementia who had dream enactment behavior [30]. According to his wife, the frequency of nocturnal episodes decreased from 6 times to 3 times per month after levetiracetam treatment (1,000 mg twice daily). Concurrent medications included atorvastatin, escitalopram, aspirin, fexofenadine, folate, and vitamin B12. The patient was advised to taper off levetiracetam, at which point severity and frequency of nocturnal episodes increased again to 8 times per month.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:
It is thought that low-dose levetiracetam can selectively reduce aberrant, but not basal, neural activity, resulting in improved cognitive outcomes in preclinical and clinical studies [6].

*fMRI studies*: A study discussed above in amnestic MCI patients showed that levetiracetam normalizes the hyperactivity in hippocampal regions [4]. In a retrospective fMRI study in drug-resistant temporal lobe epilepsy patients, levetiracetam also showed restoration of normal activation patterns in the temporal lobe in a dose-dependent manner [31]. Longitudinal studies are needed to establish whether the neural patterns translate to drug response [32].

*Molecular mechanisms of action*: The exact molecular mechanism of action for levetiracetam is unknown. Levetiracetam has high affinity for the presynaptic membrane protein SV2A, which is widely expressed throughout the brain including high levels in the hippocampus [1; 6]. While the role of SV2A in biological function is not completely understood, it appears to play a role in modulating calcium-dependent neurotransmitter release by multiple mechanisms with a greater effect during high activation. SV2A influences neurotransmitter release via expression and trafficking of the calcium sensor synaptotagmin and likely binds directly to synaptotagmin. SV2A also contributes to the mobilization of synaptic vesicles for release, and SV2A deletion reduces vesicle release during trains of action potentials but does not measurably affect steady-state activity. Levetiracetam binding to SV2A is likely a primary mechanism of action for its anti-epileptic effects based on the strong linear correlation between affinity to SV2A and the ability to protect against seizures in a mouse model of audiogenic seizure [1].

In addition to mechanisms for quieting overactive neurons by limiting transmitter release, levetiracetam inhibits both ryanodine and IP3 receptor-activated calcium release in hippocampal neurons [33; 34], which would be neuroprotective in the context of impaired calcium homeostasis in Alzheimer's [35; 36].

Other evidence includes beneficial effects of levetiracetam on mitochondria. SV2A is also expressed in mitochondria and levetiracetam reduces mitochondrial swelling after calcium-induced and toxin (atractyloside)-induced opening of the mitochondrial permeability transition pore (mPTP) [37].

Levetiracetam may also act on astrocytic SV2A. In a human astrocyte culture study, levetiracetam inhibited Aβ-induced vesicular glutamate release and thus may underlie, at least in part, the ability of levetiracetam to reduce hyperexcitability in Alzheimer disease [38].

*Models of Alzheimer's disease*: Levetiracetam has shown benefit in several mouse models of Alzheimer's disease.

In the APPswe/PS1dE9 mice, levetiracetam (50 mg/kg, i.p.) alleviated behavioral deficits and reduced amyloid plaques while increasing Aβ clearance and up-regulating Aβ transport and autophagic degradation [39]. Levetiracetam also inhibited Aβ generation, suppressed γ-secretase activity, and inhibited GSK-3β activation, while increasing AMPK/Akt activation. Levetiracetam also inhibited histone deacetylase activity *in vivo*.

In the hAPPJ20 mice, levetiracetam reduced abnormal spike activity detected by EEG, and reversed hippocampal remodeling, behavioral abnormalities, synaptic dysfunction, and deficits in learning and

memory [40]. However, prolonged levetiracetam treatment did not alter Aβ levels in the hippocampus. Levetiracetam did not improve these measures in normal mice.

In contrast to benefits observed in the studies above, levetiracetam treatment (10-20 mg/kg) was not able to rescue memory deficits in 5XFAD transgenic mice harboring amyloid plaque pathologies at moderate (6-8 months) or high (12-15 months) levels [41]. This was in contrast to levetiracetam ameliorating memory impairments of aged C57BL/6 mice (17-20 months) in the contextual fear conditioning paradigm. Acute levetiracetam immediately after training was also efficacious in rescuing contextual memory decline in aged mice, whereas administration at a later post-training interval (3 hours) had no effect.

***APOE4 interactions***: In a double-blind randomized placebo-controlled trial (named HOPE4MCI study) of 164 people with mild cognitive impairment due to Alzheimer's disease, extended-release low-dose levetiracetam (AGB101; 220 mg, orally every morning, once daily) for 18 months showed numerically greater effects on the cognitive/functional composite score, CDR-SB, in APOE4 noncarriers compared to APOE4 carriers [15]. Numerically, this corresponds to 40% less change/decline in the CDR-SB after 18 months of AGB101 treatment compared to placebo in APOE4 noncarriers; however, this difference was not statistically significant. Among APOE4 carriers, there were no numeric or statistical differences on any primary or secondary measure between AGB101 and placebo arms. Larger studies are needed to explore whether AGB101 affects APOE4 carriers and noncarriers differently.

**Aging and related health concerns:** Although a few case studies suggested relief from peripheral neuropathy, meta-analyses have failed to find significant benefits.

*Types of evidence:*

- 5 meta-analyses or systematic reviews
- 2 observational studies
- 1 case study of 3 patients with neuropathic pain
- Numerous laboratory studies

***Neuropathy***: MIXED.
In a 2014 Cochrane meta-analysis of 6 double-blind randomized controlled trials with a total of 344 patients with neuropathic pain, there was insufficient data to conclude whether levetiracetam (2,000-3,000 mg/day) was effective in reducing neuropathic pain [42]. This was partly due to the outcome

measures used, which were mostly subjective (e.g., participant-reported pain relief, Global Impression of Change). Also, this meta-analysis included patient populations of different types of neuropathic pain: central pain due to multiple sclerosis, pain following spinal cord injury, painful polyneuropathy, central post-stroke pain, post-herpetic neuralgia, and post-mastectomy pain. It is not known whether levetiracetam may be beneficial in some or all types of neuropathy.

In a 2022 Bayesian network analysis of 20 randomized controlled trials including a total of 1,198 patients with neuropathic pain after spinal cord injury, the effects of 11 different drugs on 5 outcomes were evaluated [43]. No significant differences were found among drugs (BTX-A, gabapentin, pregabalin, amitriptyline, ketamine, lamotrigine, duloxetine, levetiracetam, tramadol, carbamazepine, cannabinoids) with regard to pain relief. Levetiracetam did not produce a significantly different outcome when compared to placebo and was generally reported to be minimally effective in the treatment of spinal cord injury-related neuropathic pain. Network meta-analysis results on the efficacy of pain relief at 4-week follow-up found that BTX-A was ranked first, followed by ketamine, amitriptyline, lamotrigine, pregabalin, duloxetine, gabapentin, tramadol, levetiracetam, carbamazepine, and cannabinoids.

In a case study of 3 patients with neuropathic pain, levetiracetam treatment significantly improved pain symptoms [44]. A 55-year-old woman with bilateral sensorimotor peripheral neuropathy with axonal and demyelinating features responded to 1,500 mg twice daily levetiracetam plus nortriptyline; her pain was improved by 60%. A 75-year-old man with numbness and persistent pain in both feet for 5 years experienced complete resolution of pain with a single dose of 500 mg levetiracetam. In a 67-year-old obese male with bilateral sensorimotor peripheral neuropathy with axonal and demyelinating features, treatment with levetiracetam (1,000 mg twice daily) resulted in complete elimination of pain.

Studies in preclinical models of peripheral neuropathy also suggest benefit with levetiracetam. In a mouse model of diabetes-induced peripheral neuropathy with sciatic degeneration, levetiracetam (40 mg/kg, oral) decreased pain sensitivity while decreasing spinal expression of microglia and astrocytes [45]. In another study in a mouse model of painful diabetic neuropathy, levetiracetam (10-100 mg/kg) produced anti-nociceptive effects and the combination of levetiracetam with aspirin, ibuprofen, or paracetamol produced further benefit, suggesting synergism between levetiracetam and ibuprofen/aspirin/paracetamol in this model [46]. In a rat model of diabetic neuropathy, treatment with levetiracetam (300 or 600 mg/kg, i.p.) significantly attenuated inflammation and fibrosis in sciatic nerves and suppressed the increases in apoptosis markers (bax, caspase 3, caspase 8) and prevented the reduction in NGF expression [47].

***Glioblastoma***: UNCLEAR.
Glioblastoma is the most common malignant primary tumor of the central nervous system. The standard of care for glioblastoma is cytoreductive surgery followed by adjuvant radiotherapy and temozolomide chemotherapy [48]. The O6-methylguanine-DNA methyltransferase (MGMT) gene encodes a DNA-repair protein that abrogates the effects of temozolomide [49]. Agents that can inactivate MGMT may increase the anti-cancer potency of temozolomide. Studies have reported that levetiracetam inhibits MGMT transcription in glioblastoma and enhances apoptosis with temozolomide [50].

In a meta-analysis of 20 studies including a total of 5,804 patients with glioblastoma, levetiracetam treatment (in 1,923 patients) did not significantly improve survival, though there was significant heterogeneity across studies [51]. Levetiracetam treatment effect decreased with greater rates of MGMT methylation, suggesting that levetiracetam may be better suited for treating specific molecular/genetic profiles of glioblastoma. Further studies are needed to identify patients most likely to benefit from levetiracetam.

***Atherosclerosis***: POTENTIAL HARM/MIXED.
In a prospective longitudinal study of 109 patients with epilepsy, levetiracetam treatment (500 mg/day initially, then increased to reach maximal tolerable dose with good seizure control) for 6 months significantly increased LDL-C (from 90.2 to 98.5 mg/dl; 9.2% increase), homocysteine (from 7.9 to 10.4 µm; 31.6% increase), apolipoprotein B (from 63.6 to 77.4 mg/dl; 21.7% increase), and apolipoprotein B/A1 ratio (from 0.51 to 0.61) [52]. There were no significant changes in total cholesterol, triglyceride, HDL-C, lipoprotein(a), or vitamin B12. These findings suggest that treatment with levetiracetam might be associated with alterations in circulatory markers of vascular risk, which could contribute to the acceleration of atherosclerosis and increased risk of vascular diseases. The possible increase in atherogenecity associated with levetiracetam is not dependent on the CYP system or deficient cofactors for homocysteine metabolism (B12, etc.) and remains to be elucidated.

In contrast to the above findings, in an observational study of medical records including 2,144 patients with cerebral infarction (of whom 150 developed epilepsy), levetiracetam treatment did not alter total cholesterol, LDL-C, HDL-C, or triglyceride levels—levels were neck-to-neck to those of controls (untreated) [53]. They did find that other anti-epileptics such as carbamazepine and phenytoin significantly increased serum total cholesterol and LDL-C levels compared to baseline and untreated controls.

***Bone health***: ASSOCIATED WITH DECREASED SERUM CALCIUM.

Older anti-epileptic drugs as well as some of the newer ones have been associated with decreased bone mineral density. In a 2024 meta-analysis of 13 observational studies including a total of 612 patients with epilepsy, levetiracetam treatment was significantly associated with decreased serum calcium (standardized mean difference=-0.47; 95% CI, -0.77 to 0.16; p=0.04), but changes in bone mineral density (lumbar spine or femoral neck) were not significant [54]. Changes in other markers related to bone health, including serum phosphorus, 25-hydroxyvitamin D, alkaline phosphatase, and parathyroid hormone, were not significantly associated with levetiracetam use. Of the 13 observational studies, 6 studies were in children and 7 were in adults. A consensus has not been reached regarding the effects of levetiracetam on bone mineral density. Regular monitoring of serum calcium and other bone metabolism biomarkers may be recommended with long-term levetiracetam treatment.

**Safety:** Levetiracetam is well-tolerated but is associated with somnolence, fatigue, dizziness, irritability, and infections. There are major drug interactions with pain killers and caffeine. Levetiracetam may also increase the risk of rhabdomyolysis.

*Types of evidence:*

- 6 meta-analyses including 2 Cochrane meta-analyses
- 5 randomized controlled clinical trials
- 6 open-label studies
- 2 case studies

Levetiracetam is generally well-tolerated, and the most common adverse events include somnolence, asthenia (physical weakness), infection, and dizziness (incidence ≥5% more than placebo)(Drugs.com). However, there are some warnings and precautions around behavioral abnormalities, including suicidal ideation, irritability, and aggressive behavior.

***Clinical studies***: Numerous meta-analyses have examined the adverse events resulting from levetiracetam, though most studies have been in patients with epilepsy/seizures.

A 2015 meta-analysis of 26 randomized controlled trials including 2,832 patients was specifically focused on outcomes related to safety and adverse events ([55]). Doses ranged from 1,000-4,000 mg/day, with most studies testing 3,000 mg/day. Treatment durations ranged from 6-24 weeks. Somnolence, asthenia/fatigue, dizziness, nervousness/irritability, and nasopharyngitis were significantly associated with levetiracetam treatment. In addition, levetiracetam was significantly associated with an increased

risk of adverse event-related withdrawals. However, no dose-response relationship was found for any of the assessed variables.

In a 2024 meta-analysis of 16 randomized controlled trials including a total of 545 participants in various study populations (focal seizures, history of drug abuse, amnestic mild cognitive impairment, alcohol use disorder, Alzheimer's disease, schizophrenia, mania, healthy people, elderly people, and people with asthma on corticosteroids), levetiracetam treatment (dose ranging from 250 to 2,000 mg daily or based on body weight) was significantly correlated with somnolence, in line with previous studies [7].

Utilizing real-world data from the FDA Adverse Event Reporting System database, levetiracetam treatment significantly increased risk of rhabdomyolysis (reporting odds ratio=13.5), a condition that causes skeletal muscle to break down, leading to muscle death [56]. The study extracted adverse events related to levetiracetam from 2013 to 2024. Most adverse events occurred within the first 30 days of treatment, with a bimodal onset distribution. Men showed a higher incidence. Co-administration of antibiotics, antipsychotics, and proton pump inhibitors elevated the risk, while other antiseizure medications did not. Because this study is a retrospective analysis, it cannot control for confounding factors or establish a direct cause-and-effect relationship between levetiracetam and rhabdomyolysis. It is currently unknown how levetiracetam may be increasing the risk of rhabdomyolysis.

***In epilepsy/seizure patients***: A 2012 Cochrane meta-analysis of 11 randomized controlled trials including 1,861 subjects with drug-resistant focal epilepsy also reported that levetiracetam (add-on therapy of 1,000-4,000 mg/day in adults, 60 mg/kg/day in children) treatment for 12-24 weeks was associated with increased incidences in somnolence (RR=1.51; 99% CI 1.06 to 2.17) and infection (RR=1.76; 99% CI 1.03 to 3.02) in adults [8]. No adverse effect was significantly associated with levetiracetam in children, but changes in behavior were observed, including hostility, nervousness, aggression, agitation, irritability, "abnormal behavior", altered mood, and anxiety. The 5 most common adverse effects (any age) were: somnolence: affected 14% of subjects (RR=1.58; 99% CI 1.14 to 2.18); headache: affected 10% of subjects (RR=0.95; 99% CI 0.65 to 1.39); fatigue (asthenia): affected 8% of subjects (RR=1.53; 99% CI 0.98 to 2.38); accidental injury (lower incidence with levetiracetam): affected 8% of subjects (RR=0.72; 99% CI 0.49 to 1.06); dizziness: affected 7% of subjects (RR=1.63; 99% CI 0.99 to 2.66). In adults, only the RRs for somnolence (RR=1.51; 99% CI 1.06 to 2.17) and infection (RR=1.76; 99% CI 1.03 to 3.02) remained statistically significant with levetiracetam over placebo.

***In neuropathic pain patients***: In a 2014 Cochrane meta-analysis in patients with neuropathic pain, the amount of data was limited (6 double-blind randomized controlled trials with 344 subjects total), but significantly more subjects experienced an adverse event with levetiracetam compared to placebo [42].

***In Alzheimer's patients***: In a randomized controlled trial of 95 patients with seizures and Alzheimer's disease, patients on levetiracetam therapy (500 mg/day initially, increased every week by 500 mg/day) reported mainly central nervous system-related and mild adverse events [27]. None of the patients had clinically significant changes from baseline in hematological, urinary, and biochemical parameters. There was no evidence of idiosyncratic side effects. Adverse effects, including somnolence (2), asthenia (2), headache (1), and dizziness (1), were observed in 6 (17%) patients. However, in general, tolerability was favorable, with transient adverse effects. No adverse events required discontinuation of treatment. No patients withdrew because of side effects.

In a prospective open-label study of 25 patients with advanced Alzheimer's and late-onset seizures, 16% discontinued from levetiracetam treatment (1,000-1,500 mg/day) due to adverse events, though the types of events were not discussed [57].

In a double-blind randomized controlled crossover proof of concept study (ILiAD study) of 8 mild to moderate Alzheimer's disease patients, levetiracetam treatment for 12 weeks was well-tolerated, with no detrimental effects on mood or quality of life [25]. No participants withdrew from the study and there was no significant difference in reported side effects between the levetiracetam and placebo arms. Headache was the most frequently reported event. There were no serious adverse reactions reported in the study.

***In people with mild cognitive impairment***: In a double-blind randomized placebo-controlled trial (HOPE4MCI study) of 164 people with mild cognitive impairment due to Alzheimer's disease, extended-release low-dose levetiracetam (AGB101; 220 mg, orally every morning, once daily) for 18 months was generally well-tolerated [15]. The overall incidence of treatment-emergent adverse events was similar in the AGB101 and placebo arms (67.9% and 71.1%, respectively). The most common adverse events (affecting more than 5% of the participants) in the AGB101 group were urinary tract infection (6.4% with AGB101 and 3.6% with placebo), fall (7.7% with AGB101 and 9.6% with placebo), and anxiety (5.1% with AGB101 and 2.4% with placebo). Treatment-emergent adverse events leading to discontinuation of the trial agent occurred in 7.7% of the participants in the AGB101 group and 3.6% of those in the placebo group.

***In elderly patients with epilepsy***: In a randomized unblinded superiority study testing levetiracetam and other antiepileptics in 308 elderly patients with newly diagnosed epilepsy, adverse events were reported by 76.2% of patients treated with levetiracetam [58]. Discontinuation rates due to adverse events were 11.3%. Higher severe adverse events were reported in the levetiracetam (20.5%) and carbamazepine (17.5%) groups compared to those treated with sodium valproate (8.2%). The most common adverse events were fatigue (11.3%) with levetiracetam.

In a small open-label phase 4 prospective study, 24 elderly patients with cognitive impairment and seizures were treated with levetiracetam (250 mg twice daily at first, then increased every 3 days until desired dose) for 12 weeks, and fatigue was the most common side effect (20.8%; 5 participants) [16]. One subject experienced loss of balance and dizziness but did not discontinue levetiracetam. There were no reports of insomnia, headache, anorexia, or weight loss.

***In patients with brain tumors and seizures***: In a prospective open-label study of 20 patients with brain tumors and seizures, levetiracetam (500 mg i.v. twice daily following surgery, then titrated by 500 mg/day increments up to a max dose of 3,000 mg/day) treatment was safe and well tolerated with no medication discontinuation during the study period [59]. Adverse effects reported were somnolence, nausea/vomiting, headache, and insomnia.

***In patients with brain injury***: In a 2022 network meta-analysis of randomized and non-randomized controlled trials, various anti-seizure medications (phenytoin, phenytoin + phenobarbital, levetiracetam, phenytoin + levetiracetam, lacosamide, valproate) were evaluated for the prevention of seizures in brain injury patients [19]. Patients treated with levetiracetam (and valproate) had higher mortality than those treated with placebo. Levetiracetam also had higher treatment-related adverse event incidence than placebo. In the network meta-analysis, phenytoin had the highest rate of treatment-related adverse effects, followed by levetiracetam, placebo, and lacosamide.

***Case study of levetiracetam overdose***: There was one case study of a 43-year-old female who overdosed with 60-80 grams of levetiracetam (along with 20 tablets of paracetamol/codeine and unknown quantity of alcohol) [60]. She experienced mild central nervous system depression, bradycardia, hypotension (86/57), and oliguria (low production of urine). Her cardiovascular toxicity transiently responded to atropine and intravenous fluids. An echocardiogram demonstrated normal left and right ventricular contractility. Despite her cardiovascular toxicity and oliguria, she had normal serial venous lactates and renal function, and made a complete recovery over 48 hours. Her levetiracetam concentration was 463 µg/ml 8 hours post-ingestion (therapeutic range 10-40 µg/ml). Levetiracetam in

large amounts appears to cause bradycardia and hypotension that is potentially responsive to atropine and intravenous fluids. Based on a normal echocardiogram, levetiracetam at high concentration may have acted at muscarinic receptors.

***Patient ratings***: Levetiracetam has an average rating of 5.8 out of 10 from a total of 420 reviews on Drugs.com. The majority of reviews are from people with seizures (242 reviews) and epilepsy (161 reviews), with 44% of reviewers reporting a positive experience and 33% reporting a negative experience.

***Drug interactions***: Levetiracetam has major drug interactions with 6 drugs: brexanolone, buprenorphine, esketamine, ketamine, propoxyphene (narcotic pain-reliever), and sodium oxybate (treatment for narcolepsy) (Drugs.com). It also has moderate drug interactions with 229 drugs (Drugs.com). Alcohol can increase the nervous system side effects of levetiracetam such as dizziness, drowsiness, and difficulty concentrating. The clearance of levetiracetam is decreased in patients with renal impairment (Drugs.com). Levetiracetam should be administered cautiously at reduced dosages in people with impaired renal function. The use of levetiracetam may be associated with minor decreases in total red blood cell count, hemoglobin, and hematocrit. Levetiracetam should be administered cautiously in patients with or predisposed to anemia or neutropenia.

Levetiracetam treatment may also increase the risk of rhabdomyolysis, a condition that causes skeletal muscle to break down, leading to muscle death [56]. Co-administration of antibiotics, antipsychotics, and proton pump inhibitors elevated the risk, while other antiseizure medications did not.

In a case study of an early adolescent male with epilepsy, a combination therapy with lamotrigine (anti-epileptic drug) and levetiracetam was associated with toxic optic neuropathy and progressive bilateral painless visual loss [61]. Macula optical coherence tomography (OCT) showed mild retinal ganglion cell loss in all inner quadrants. The visual loss was resolved with cessation of lamotrigine, not levetiracetam.

**Sources and dosing:**

Levetiracetam is a prescription medication and comes in tablet (250, 500, 750, and 1,000 mg) and solution (500 mg/mL, 100 mg/mL) forms. For treatment of epilepsy, doses are started low (e.g., 250 mg twice daily), then increased until the desired effect (e.g., seizure control) is achieved. Clinical studies in epilepsy patients have used doses ranging from 1,000-3,000 mg/day. Clinical trials in mild cognitive

impairment and Alzheimer's disease are testing lower doses (220-1000 mg/day, orally)(NCT05986721; NCT03875638).

A low-dose extended-release oral formulation of levetiracetam, AGB101, has been formulated by AgeneBio, Inc. In people with mild cognitive impairment, AGB101 dose of 220 mg, orally, once daily, has been tested [15].

**Research underway:**

According to ClinicalTrials.gov, there are 39 clinical studies currently ongoing that are testing levetiracetam. Three studies are in Alzheimer's disease patients (with or without epilepsy) (NCT04004702; NCT03875638; NCT05969054), one is in mild cognitive impairment (NCT05986721), and two are in Parkinson's disease patients (NCT05824728; NCT04643327).

The study in mild cognitive impairment is a randomized double-blind placebo-controlled study testing a low-dose formulation of levetiracetam (AGB101, 220 mg) once daily for 78 weeks in 60 participants (NCT05986721). Primary outcomes are change in entorhinal cortex volume from baseline and cognitive/functional composite (CDR-SB). This study is scheduled to be completed in December 2028.

A double-blind placebo-controlled crossover study is testing low-dose levetiracetam (125 mg or 500 mg twice daily) for 4 weeks in 85 people with Alzheimer's disease (NCT03875638). This study is scheduled to be completed in November 2024.

Other clinical trials are testing levetiracetam in patients with seizures, brain tumors, schizophrenia, panic disorder, psychosis, traumatic brain injury, and others.

**Search terms:**

Pubmed, Google:

- + cognitive, + Alzheimer's, + APOE, + meta-analysis, + Cochrane, + lifespan, + cardiovascular, + neuropathy, + diabetes, + atherosclerosis

Websites visited for levetiracetam:

- Clinicaltrials.gov

- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)

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