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.

Piracetam

Evidence Summary
Piracetam benefits cognitive functions in older adults, though many of the studies are old and the quality suboptimal. It does interact with anticoagulants and thyroid extracts.

**Neuroprotective Benefit:** Several studies have shown that piracetam benefits cognitive functions in older individuals but not in dementia patients. Despite the numerous clinical trials, many are old and did not use sophisticated measures.

**Aging and related health concerns:** No studies have tested whether piracetam prevents age-related diseases, though piracetam intervention pre- and post-surgery reduced postoperative cognitive decline in heart surgery patients.

**Safety:** Piracetam is well tolerated, but it does interact with anticoagulants and thyroid extracts and people with suspected kidney problems or bleeding problems should talk to their doctor before taking piracetam.
### What is it?

Piracetam is a nootropic and the parent compound of the racetam drug class. It was first marketed by UCB Pharma in Belgium in 1971, but in the US, it is not approved for any medical use and it is not permitted to be sold as a dietary supplement (DrugBank). In the UK, piracetam is prescribed for myoclonus (involuntary spasmodic contraction of muscles), but it is used off-label for learning difficulties in children and cognitive deficits in the elderly. Piracetam modulates the cholinergic, serotonergic, noradrenergic, and glutamatergic neurotransmission (DrugBank). It does not have high affinity to any of the neurotransmitter receptors, but it does bind to the glutamate receptor subunit GluA2 [1]. Piracetam interacts with the polar heads of phospholipids making up the plasma membrane and influences membrane function and fluidity.

### Neuroprotective Benefit:

Several studies have shown that piracetam benefits cognitive functions in older individuals but not in dementia patients. Despite the numerous clinical trials, many are old and did not use sophisticated measures.

### Types of evidence:

- 8 meta-analyses in various patient populations
- 8 randomized controlled clinical trials
- 1 PET imaging study in dementia patients
- Numerous laboratory studies

<table>
<thead>
<tr>
<th>Availability: Not OTC</th>
<th>Dose: 1,200-4,800 mg per day in adults</th>
<th>Chemical formula: C₆H₁₀N₂O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life: 5 hours in young adult men</td>
<td>BBB: penetrant</td>
<td>MW: 142.158</td>
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<tr>
<td>Clinical trials: Largest meta-analysis included 24 DBRCTs including a total of 11,959 subjects (half of whom received placebo)</td>
<td>Observational studies: none</td>
<td>Source: PubChem</td>
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Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

**Aged individuals:** POTENTIAL BENEFIT. Many of the clinical trials are from the 70's and 80's and some of the outcome measures were subjective. In a double-blind controlled crossover study of 18 normally aged individuals, piracetam treatment (1.6 g x 3 times daily) for 4 weeks was associated with significantly better performance on the Digit Symbol Test, Bourdon-Wiersma Test (visual perception), Spoke Test (similar to trail making test), Critical Flicker Fusion (visual function), and Krakau Visual Acuity Test [2]. In a larger double-blind controlled trial of 50 geriatric patients, piracetam treatment (2.4 g/day) did not show statistically significant differences compared to controls in 10 different cognitive tests. However, on Clinical Global Evaluation, 52% of the patients on piracetam showed minimal improvement versus 25% of the patients in the placebo group [3].

**Cognitively impaired older adults:** BENEFIT. In a 2002 meta-analysis of 19 double-blind randomized controlled trials including a total of 1,489 older adults with cognitive impairment, piracetam treatment (2.4-8.0 g/day; duration ranged from 6 weeks to 52 weeks, mostly 6-12 weeks) was associated with improvement in clinical assessment [4]. The comparison was "piracetam better" vs "placebo better" and the magnitude of change could not be measured as most studies (12/19) used Clinical Global Impression (a 7-point scale) as their sole outcome; only 7 studies also used psychometric assessments. In the placebo arm, 227 improved (34.1%) and 438 (65.9%) experienced no change or got worse. In the piracetam arm, 481 improved (63.9%) while 272 (36.1%) showed no change or got worse.

In a double-blind controlled study (not included in the above meta-analysis) in 60 elderly psychiatric patients with mild cerebral impairment, piracetam treatment for 12 weeks improved overall functioning, particularly alertness, socialization, and cooperation, relative to the control group [5]. Patients treated with 2.4 g/day piracetam showed significant improvement in scores for the full IQ and the memory quotient on the Wechsler Adult Intelligence and Memory Scales; greater response was seen in those with lower initial scores. Piracetam at 4.8 g/day had a more rapid onset of action on behavioral variables than 2.4 g/day, but its therapeutic effect tended to diminish at 12 weeks, possibly because of overstimulation. Piracetam did not appear to interfere with concomitant psychotropic maintenance medication or affect the psychiatric illness itself.

**Vascular cognitive impairment:** UNKNOWN. Based on a 2017 review on vascular cognitive impairment, benefits of piracetam are not clear [6]. There have not been any well-designed studies that have demonstrated convincing evidence to support routine use of piracetam.
**Stroke patients**: SOME BENEFIT. In a meta-analysis of 7 randomized controlled trials in post-stroke patients, piracetam treatment (mostly 4.8 g/day; duration ranged from 2 weeks to 6 months) did not improve overall severity of aphasia, but the treatment was associated with pronounced improvement in written language [7]. The study also noted that piracetam’s effects on overall linguistic level and written language tended to emerge within a short period and declined in longer therapy.

**TBI patients**: UNKNOWN. In a meta-analysis of clinical or observational studies in patients with traumatic brain injury that examined various therapeutics (e.g., cerebrolysin, citicoline, piracetam), there was not enough available research to gauge the effects of piracetam in TBI management [8].

**Children**: MIXED. In a meta-analysis and clinical practice guideline for children with reading or spelling disorders in children and adolescents, they recommended against the use of piracetam [9]. In a randomized controlled trial of 250 children undergoing general anesthesia, intravenous piracetam (30 mg/kg) prevented postoperative cognitive dysfunction, though the full text was not accessible so the extent of cognitive improvement/preservation could not be evaluated [10].

_Human research to suggest benefits to patients with dementia:_

**Alzheimer’s dementia**: LACK OF BENEFIT. In a double-blind randomized controlled trial of 33 probable Alzheimer’s patients, high dose piracetam (8 g/day, orally) for 1 year did not result in improvement in cognitive functions [11]. The full text for this study was not accessible so the results could not be fully evaluated.

In a small double-blind crossover trial of 18 Alzheimer’s patients, piracetam treatment (2.4-9.9 g/day), either alone or in combination with phosphatidylcholine (18 g/day), did not significantly affect cognition as a whole, nor did it improve test performance in any single patient [12]. The link to the full text for this study was broken so details could not be evaluated.

In an even smaller double-blind crossover trial of 11 Alzheimer’s patients, piracetam (4.8 g/day) + lecithin (35 g/day) treatment for 3 months showed that 8 out of 11 patients showed various degrees of improvement compared to the placebo phase [13]. The remaining patients did not improve or worsened during the active phase. Piracetam plus lecithin may ameliorate selective memory deficits in some patients. Nonresponders had little or no aphasia.
**Parkinson’s/Lewy body dementia:** LACK OF BENEFIT. In a meta-analysis of 44 different studies in Lewy Body Dementia, only 1 tested the effect of piracetam [14]. It was a double-blind randomized controlled trial of 20 people with Parkinson’s dementia, and patients were treated with piracetam (3.2 g/day for 12 weeks followed by 4.8 g/day for an additional 12 weeks) or placebo [15]. Twenty-five percent of the patients did not complete the trial for reasons unrelated to the medication. Although there was a significant improvement on one subtest (functional capacity measured by the Sickness Impact Profile) of the functional scale, no significant effects were demonstrated in cognitive or neurological measures. There is no evidence that piracetam changes any motor or cognitive aspect of Parkinson’s.

**Nonspecific/unclassified dementias:** MIXED. In a 2001 Cochrane meta-analysis of 24 double-blind randomized controlled trials with a total of 11,959 subjects total, no significant differences were found between piracetam treatment (2.4-9.6 g/day; duration ranged from 1 week to 1 year) and placebo groups for cognition (immediate memory, visuospatial, Mini Mental Status Examination [MMSE], delayed memory or speech), for dependency, or for depression [16]. Though using a fixed-effect model, the odds ratio for improvement with piracetam compared with placebo was 3.55 (95% CI, 2.45 to 5.16). Although effects were found on Global Impression of Change, no benefit was shown by any of the more specific measures of cognitive function. Further evaluation of piracetam is needed. Piracetam was one of the first drugs used for dementia and comes from the class of drugs called nootropics, whose putative actions are still poorly defined. Most of the trials of piracetam were undertaken many years ago and did not use methods which would be currently considered standard. Some of the studies suggested there may be some benefit from piracetam but overall the evidence is not consistent or positive enough to support its use for dementia or cognitive impairment. The mean difference for MMSE (1 study, 30 subjects) was 1.8 (-3.29 to 6.89). The mean difference for Global Scale was 0.27 (-0.62 to 1.17).

In a phase III double-blind randomized controlled trial in 130 patients with dementia (for at least 2 years), piracetam treatment (4.8 g/day) for 3 months showed statistically significant “explorative response rates” of 50% and above in 3 out of 4 target variables (e.g., Clinical Global Impression, Sandoz Clinical Assessment Geriatric, etc.) as compared to the 0-6% obtained with placebo [17]. The full text was not accessible for this paper.

**Mechanisms of action for neuroprotection identified from laboratory and clinical research:**

A PET imaging study in 9 Alzheimer’s and 7 unclassified dementia patients reported that piracetam treatment (6 g, twice daily) for 2 weeks significantly improved cerebral glucose metabolism in most cortical areas (frontal, central, parietooccipital, visual, auditory, and cingulate cortex) in Alzheimer’s...
patients, whereas no effect was observed in the multi-infarct dementia/unclassified dementia groups [18]. The results suggest that the typical metabolic depression in Alzheimer's disease is caused by complex interactions of disturbed transmitter and cellular function rather than by a specific deficit in the cholinergic system alone. While the results were positive, it was a small study and the data are preliminary.

In rodents, piracetam treatment prevented memory impairment induced by scopolamine [19] and reversed inflammation (LPS)-induced spatial memory impairment [20]. These studies also showed that piracetam decreased oxidative stress (lipid peroxidation, nitrite levels), prevented the increase in neuroinflammation (IL6), and increased blood levels of Aβ suggesting greater efflux of Aβ from the brain to the blood [20].

The mechanism of action for piracetam is that it enhances the fluidity of plasma membranes by interacting with the polar heads of phospholipids. Piracetam also increases fluidity of brain mitochondrial membranes and several studies have shown that piracetam enhances mitochondrial membrane function, ATP production, and reduces sensitivity to apoptosis [21]. In cell culture systems, piracetam also inhibited the opening of the mitochondrial permeability transition pore, which forms under mitochondrial stress and can lead to mitochondrial swelling and apoptosis [22]. In rats injected with rotenone (pesticide that interferes with the electron transport chain in mitochondria), pretreatment with piracetam significantly protected against oxidative stress, though this benefit was not seen when piracetam was given at the same time as rotenone [23].

In model plasma membranes, piracetam significantly decreased the harmful destabilizing effect of Aβ by coating the phospholipid headgroups [24].

**APOE4 interactions:** No studies have examined the effects of piracetam based on APOE status.

**Aging and related health concerns:** No studies have tested whether piracetam prevents age-related diseases, though piracetam intervention pre- and post-surgery reduced postoperative cognitive decline in heart surgery patients.

**Types of evidence:**
- 3 meta-analyses, 2 in stroke patients and 1 in heart surgery patients
- Several laboratory studies
Stroke: LACK OF BENEFIT. No studies have examined whether piracetam may prevent stroke, but several clinical trials have tested piracetam in people who have already experienced stroke. A meta-analysis of randomized controlled trials (RCTs) in stroke patients reported that there is insufficient evidence for the use of piracetam (3 RCTs) in promoting recovery from stroke [25].

In a 2012 Cochrane meta-analysis of 3 RCTs in acute ischemic stroke, piracetam was associated with a non-significant increase in death at one month (approximately 31% increase, 95% CI, -5% to 81%) [26]. There were 1,002 patients total in this meta-analysis, but 1 trial contributed to 93% of the data. The trend for increased death was no longer apparent in this large trial after correction for imbalance in stroke severity. Limited data showed no differences between the treatment and control groups for functional outcome, dependence, or proportion of patients who were dead/dependent. Although there was a suggestion of an unfavorable effect of piracetam on early death, this was confounded by baseline differences in stroke severity in the trials.

Cardiovascular: POTENTIAL BENEFIT. No studies have tested whether piracetam may prevent cardiovascular disease, but a few randomized controlled trials (RCTs) have tested piracetam in patients who underwent coronary bypass surgery. A meta-analysis of 3 RCTs including 282 patients undergoing coronary bypass surgery evaluated the potential benefits of high dose piracetam treatments pre- and post-surgery. For the 2 acute studies, piracetam infusion (12 g/60 ml, i.v.) prior to surgical intervention provided short-term neuroprotective effect and reduced postoperative decline of neuropsychological abilities [27]. For the third study, patients were administered 150 mg/kg i.v. piracetam prior to coronary artery bypass grafting, followed by 12 g/day oral treatment for 6 weeks. After 6 weeks of treatment, cognition was significantly improved in patients treated with piracetam compared to placebo. A statistically significant difference was identified between the piracetam and control groups in the change from baseline in 5 of the subtest scores (immediate pictured object recall, WMD=0.91, 95% CI, 0.51-1.31; delayed pictured object recall, WMD=0.74, 95% CI, 0.19-1.28; delayed picture recognition, WMD=0.82, 95% CI, 0.31-1.31; immediate word recall, WMD=0.87, 95% CI, 0.47-1.28; letter interference, WMD=-3.46, 95% CI, -5.69 to -1.23). No statistically significant difference was observed between piracetam and control in attention scores.

Peripheral neuropathy: POTENTIAL BENEFIT IN PRECLINICAL STUDIES. No studies have tested piracetam in people with peripheral neuropathy. In a rat model of peripheral neuropathic pain (by chronic constriction injury of the sciatic nerve), piracetam treatment dose-dependently improved neuropathic pain [28]. At 50 mg/kg, there were no effects, while at 100 mg/kg, rats had significantly decreased paw withdrawal duration (cold allodynia test) while no effects were seen on the hot plate and tail flick tests.
(thermal hyperalgesia tests). Piracetam at a dose of 200 mg/kg significantly modulated neuropathic pain, based on increased hot plate and tail flick latencies, as well as decreased paw withdrawal duration. The human equivalent dose for the highest dose was 32.3 mg/kg.

**Safety:** Piracetam is well tolerated, but it does interact with anticoagulants and thyroid extracts and people with suspected kidney problems or bleeding problems should talk to their doctor before taking piracetam.

**Types of evidence:**
- 2 Cochrane meta-analyses, 1 in acute ischemic stroke and 1 in painful sickle cell disease crises
- 2 double-blind clinical trials, 1 in Alzheimer’s patients and 1 in aged individuals
- 1 open-label trial in epilepsy patients
- 1 review

**Clinical studies:** Piracetam appears to be well-tolerated and very few studies reported toxic side effects, though it is possible that because some of the studies were old and of suboptimal quality, there was underreporting of adverse events.

In a 2016 Cochrane meta-analysis of 3 randomized controlled trials (RCTs) including 169 patients with painful sickle cell disease crises, i.v. infusion of piracetam (doses ranged, but during crises, 160-300 mg/kg/day) did not result in toxicity or adverse effects other than one participant who experienced dizziness [29].

A 2012 Cochrane meta-analysis of 3 RCTs including 1,002 patients with acute ischemic stroke stated that adverse effects were not reported [26].

In two double-blind controlled studies, each including 18 patients, no side effects or toxic effects were noted [2; 12]. In an open-label study of 11 subjects with progressive myoclonus epilepsy, 2 patients reported drowsiness during the first 2 weeks of piracetam treatment, though there was no relationship between the dosage and occurrence of adverse effects and none of the patients needed to discontinue treatment [30]. When starting at a low dose (3.2 g/day) and increasing gradually (max dose 20 g/day), none of the patients developed diarrhea, a common adverse effect of piracetam when given at a high dosage.
The most comprehensive information was found in a 1999 review of post-marketing surveillance reports in stroke patients [31]. The authors reviewed studies that included a total of 927 patients (464 treated with piracetam) and confirmed piracetam’s safety profile and lack of organ toxicity across its 25 years of clinical usage. Tolerance was equally high with the more recent use of larger doses (up to 24 g/day) for the long-term control of cortical myoclonus and when given intravenously to patients with acute stroke. Although death within 12 weeks occurred more often in the piracetam group (23.9%; 111/464) as compared with placebo (19.2%; 89/463), the difference was not significant after controlling for initial stroke assessment scale scores (Orgogozo scores). Factors other than treatment (piracetam) significantly contributed to death, such as severity of stroke, age, female sex, myocardial infarction, and diabetes. The adverse event profile was similar in both treatment and placebo groups, with no significant differences in the numbers of patients with adverse events, frequency of adverse events overall, or those considered serious. The types of adverse events also did not differ between groups. Nine piracetam-treated and 6 placebo-treated patients discontinued treatment because of adverse events, all considered unrelated or unlikely due to study medication. Seizures were reported in 5 piracetam-treated and 16 placebo-treated subjects.

_Treato rating:_ Treato.com rates piracetam 4.0 stars out of 5, with 3,998 positive comments compared to 2,656 negative ones as of 4/2/2018. Side effects and concerns raised included sleepiness (524), weakness (433), hypomania (219), paranoia (191), and weight gain (160).

_Drug interactions:_ Based on leaflets for Nootropil®, piracetam may interact with thyroid extract, thyroxine, anticoagulants (e.g., warfarin or acenocoumarol), and aspirin (Drugs.com). You should not take piracetam if you have ever had serious kidney problems, brain hemorrhage, or if you suffer from Huntington’s disease. People with suspected kidney problems or bleeding problems should talk to their doctor or pharmacist before taking piracetam. Piracetam is excreted in human breast milk so should not be taken by breastfeeding mothers (PubChem).

_Sources and dosing:_ Piracetam is not sold OTC. Most clinical trials have used doses of 4.8 g/day (ranging from 2.4-9.6 g/day) [4; 7; 13; 16; 17].

_Research underway:_ No clinical trials are currently testing piracetam. A study to evaluate the efficacy and safety of piracetam on aphasia after acute ischemic cerebral artery stroke was terminated after a pre-specified interim analysis (NCT01883011). There are currently 19 ongoing clinical trials testing the effects of levetiracetam, an antiepileptic drug with structural similarities to piracetam. A phase 2 trial
testing levetiracetam for Alzheimer’s disease is scheduled to be completed in December 2019 (NCT02002819).

Search terms:
Pubmed, Google: piracetam
- + cognitive, + Alzheimer’s, + ApoE, + meta-analysis, + clinical trial, + cardiovascular, + inflammation, + lifespan, + safety, + toxicity

Websites visited for piracetam:
- Clinicaltrials.gov
- Examine.com
- Treato.com
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com (no info)
- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)

References:


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