Cognitive Deficiencies

Psychiatry and neurology have, till today, nothing to offer to patients suffering from cognitive deficit. Though an attempt can be made to remove the underlying cause, the damage already done to the brain can rarely be undone. A new drug, **Piracetam** (2-pyrrolidone - acetamide) is claimed to have activation, protection, and function restoring effects on nerve cells in distress.

Experimentally, it has been reported that piracetam exerts a protection effect against audiogenic epileptic seizures in rats and the disturbing effects of ECT, senescence, alcohol intoxication and hypoxia upon learning in mice and rabbits. Further, it facilitates the learning and the memory fixation in rats. No serious toxicity was observed in previously reported evaluation in humans.

It is postulated that these effects on central nervous system are exerted directly on the cerebral cortex. The drug possesses no sedative or stimulatory effects, and does not influence behaviour; in this respect, it differs from the psychotropic agents.

It can be seen from the table that there were 13 patients on piracetam and 11 patients on placebo. In the case of patients who were on piracetam, there was no case in category of mild cognitive deficiency, there were 10 cases in moderate category, 8 of whom recovered at the end of two weeks and remaining 2 cases at the end of three weeks. All the three cases of severe category recovered at the end of 4 weeks. In the case of patients who were on placebo there were 3 cases in the category of mild cognitive deficiency, two of whom recovered at the end of one week and remaining one at the end of two weeks. There were 8 cases in moderate category; four recovered at the end of two weeks and remaining four recovered at the end of three weeks. There was no case in the severe category. All the cases had complete recovery by the end of four weeks whether on piracetam or on placebo. No side effects were noted.
When the test data was subjected to statistical analysis, no significant difference was noticed between the drug and the placebo on the recovery rate from the cognitive deficiency produced by ECT. However, if one considers only the patients suffering from moderate cognitive deficiency, it will be noted that 80% of the patients on piracetam recovered within 2 weeks whereas only 50% of those on placebo recovered in the same period, suggesting that the drug may be superior to placebo. This observation needs to be confirmed by further work.

Psychometric evaluation

According to the psychometric evaluation, the findings also confirmed the clinical observations that there was no significant difference between the drug and the placebo.

Discussion

The evaluation of drugs such as piracetam is beset with inherent difficulties. No two patients suffering from organic brain syndrome are alike; therefore, it is very difficult to get a matching control population. Similarly, the rate of natural improvement, remission, or deterioration cannot be predicted even in cerebrovascular accidents, much less in the senile dementias. The testing for cognitive deficit is also fraught with dangers as the tests have to be simple enough for the patient to understand, but sensitive enough to pick up the cognitive deficit.

ECT is known to produce cognitive deficiency similar to what is observed in organic brain syndrome. About 60% of the patients undergoing treatment with ECT develop cognitive deficiency, ranging in intensity from mild to very severe. This deficiency is usually influenced by the strength of the current, the number of stimuli, the frequency of treatment, the technique—whether bilateral or unilateral, and the condition of the brain which is subjected to this treatment. Patients usually recover from this deficiency in about 3 to
6 weeks unless its intensity is very severe in which case it might take up to a maximum of 6 months for total recovery. Till to-day there is no conclusive evidence that ECT produces any permanent damage in a healthy fully developed brain.

Various workers have studied the effect of piracetam on organic brain syndromes and have claimed favourable results. Our study shows that piracetam is not better than placebo in the recovery from cognitive deficiency.

**Piracetam for Treatment Tardive Dyskinesia**

The mechanism involved in the development of tardive dyskinesia (TD) is complicated. It now seems that several neurotransmitter systems may be affected, including dopaminergic, noradrenergic, gamma-aminobutyric acid (GABA) ergic, cholinergic and peptidergic pathways.

Piracetam (2-oxo-pyrrolidone) is a nootropic drug structurally related to GABA. It has been used clinically to treat a wide range of diseases and conditions, mainly in treatment of organic brain syndrome, myoclonus, memory impairment, post-concussional syndrome, vertigo, alcohol withdrawal, cerebrovascular insufficiency, hypoxia, intoxications of different origins or mechanic brain injures.

Piracetam is cerebral homeostatic normalizer, neuroprotectant, cerebral metabolic enhancer and brain integrative agent. It enhances brain energy, especially under deficit condition: hypoxia, chemical toxicity or impaired cerebral microcirculation; preserve, protect and enhance synaptic membrane and receptor structure and plasticity. It has various effects on glutamate neurotransmission on micromolar levels piracetam potentiates potassium-induced release of glutamate from hippocampal nerves. It is an oxidant agent and may be useful for treatment TD. Piracetam is among the toxicologically safest drugs ever developed even in mega doses.
Data derived from some clinical reports have suggested that piracetam can improve symptoms and is effective agent for treatment of different movement disorders including acute neuroleptic induced extrapyramidal symptoms and TD. The doses that used for TD treatment varied from 800 mg/day to 24000 mg/day. According to these findings the symptoms of TD disappeared in the period of 3-7 days.

To date there was only one double-blind crossover study regarding use of piracetam for treatment TD that was conducted almost 20 years ago. The findings of this study were impressive, but to our knowledge nobody reproduced these results.

**Piracetam (Nootropyl)**

Piracetam is what I refer to as “a drug in search of a disease.” A best-selling drug in Europe and Japan, a large portion of sales is to normal adults looking for cognitive enhancement. It is not a drug of first choice for any disease process yet, though current research is looking into myoclonus, sickle cell disease, strokes and Raynaud’s syndrome.

Piracetam is reported to be an intelligence booster and CNS (central nervous system) stimulant with no known toxicity or addictive properties and is inexpensive. The subjective effect described by some people is that piracetam, wakes up your brain. Its effects and safety are so impressive that piracetam prompted the creation of a new pharmaceutical category called nootropics.

The term nootropic comes from a Greek word meaning acting on the mind. Since the invention of piracetam by UCB Laboratories in Belgium, other pharmaceutical companies have been scrambling to develop their own nootropics. Some of them being researched now include; vinpocetine, aniracetam, pramiracetam, and oxiracetam.

Piracetam is very similar in molecular structure to the amino acid pyroglutamate. Piracetam and pyroglutamate have the same base.
chemical structure, the 2-oxo-pyrrolidine, but they differ by the side chain. Pyroglutamate is 2-oxo-pyrrolidine carboxylic acid, and piracetam is 2-oxo-pyrrolidine acetamide.

Piracetam enhances cognition under conditions of hypoxia (too little oxygen), and also enhances memory and some kinds of learning in normal humans. Piracetam is used to treat alcoholism, stroke, vertigo, senile dementia, sickle cell anemia, dyslexia, and numerous other health problems.

One of the most intriguing effects of piracetam is that it promotes the flow of information between the right and left hemispheres of the brain. We know that the communication between the two sides of the brain is associated with flashes of creativity. This may also be the basis for piracetam’s usefulness in the treatment of dyslexia.

The effect of piracetam can be increased if taken with DMAE, centrophenoxine, choline, or Hydergine. When choline and piracetam are taken together there is a synergistic effect that causes a greater improvement in memory than the sum of each when taken alone.

We know of one person who claims she feels slightly agitated and depressed if she takes piracetam for more than a week without a choline supplement. This feeling is alleviated for her with a single dose of choline. It may be that the piracetam causes acetylcholine to be used up more quickly and that the choline helps to replace this important neurotransmitter.

One fascinating study suggests that piracetam might increase the number of cholinergic receptors in the brain. Older mice were given piracetam for two weeks and then the density of muscarinic cholinergic receptors in their frontal cortexes was measured. The researchers found that these older mice had 30-40% higher density of these receptors than before. Piracetam, unlike many other drugs, appears to have a regenerative effect on the nervous system.
One theory of Alzheimer’s disease is that the decline of intellectual functions is partly caused by a decreased activity of the cholinergic system in the brain caused by cell death and cell degeneration. The researchers in the above study speculated that their findings could explain how piracetam works and could also explain the finding regarding a profound effect of combining choline with piracetam on memory enhancement of old rats.

As mentioned previously the late drug researcher Arthur Cherkin related to us that he believed the combination of Hydergine and piracetam potentiate each other by five times. This highlights the importance of adjusting the dosage when multiple substances are taken because; some of these substances will cause paradoxical effects when excessive amounts are taken.

Although piracetam is a derivative of GABA (gamma amino butyric acid, a neurotransmitter), there is no evidence that piracetam works through the GABAergic system. Some research even suggests GABA may even inhibit memory and learning.

Precautions: Piracetam may increase the effects of certain drugs, such as amphetamines, psychotropics, and Hydergine, as stated. Adverse effects are rare but include insomnia, psychomotor agitation, nausea, gastrointestinal distress, and headaches. Piracetam has virtually no known toxicity or contraindications.

Dosage: Piracetam is supplied in 400 mg or 800 mg capsules or tablets. The usual dose is 2400 to 4800 mg per day in three divided doses. Some literature recommends a high attack dose be taken for the first two days. We have noticed that often when people first take piracetam they do not notice any effect at all until they take a high dose (approximately 4000 to 8000 mg). Thereafter, they may notice that a lower dosage is sufficient. Piracetam takes effect within 30 to 60 minutes.
Piracetam and Dyslexia


2. Volavka J et al. *Effect of piracetam on EEG spectra of boys with learning disorders.* Psychopharm 72: 185-188, 1981. Studied EEG changes by piracetam on 30 children with learning disorders. Changes in delta waves, no change between left and right hemispheres. Same effect as seen with amphetamines. (Note: learning disorders are associated with EEG slowing, and the effect of piracetam is similar to that of Ritalin per these authors.)

3. Ackerman PT et al. *A trial of piracetam in two subgroups of students with dyslexia.* J Learning Disab 24(9): 542-549, 1991. 53 children with dyslexia, categorized as dysphonetic (could not associate sounds with phonic representations) or phonetic (could associate). Piracetam helped phonetic group improve word recognition; no other differences noted. Both groups given tutoring with the piracetam.


Piracetam and Senile Dementia

with placebo study on patients in nursing home. Attention improved, no other effects seen.

2. Faleni J Pharmacol 5(30), 1974 80% of senile dementia patients showed improvement after piracetam treatment for 11 weeks.

3. Friedman E et al. *Clinical Response to choline plus piracetam in senile dementia: relation to red-cell choline levels*. New Eng J Med 1981 Jun 11; 304(24): 1490-1. This is actually a “letter” rather than a full paper, and consisted giving 10 patients with presenile dementia piracetam and choline for 7 days in a non-controlled study. 3 of the 10 had “marked improvement” cognitively, but no description of the cognitive tests or whether the testing was blinded is mentioned. The 3 who responded had higher choline red blood cell levels than the 7 who did not respond.


5. Growdon JH et al. *Piracetam combined with lecithin in the treatment of Alzheimer's disease*. Neurobiology of Aging 7:269-276, 1986. Piracetam was administered alone or with lecithin (phosphatidylcholine) in a double-blinded test. No effect was seen, with or without lecithin, on cognition or memory test scores.

6. Corona GL et al. *Clinical and biochemical responses to therapy in Alzheimer's disease and multi-infarct dementia*. Eur. Arch. Psychiatr. Neurol. Sci. 239:79-86, 1989. Patients with either AD or multi-infarct dementia were given either piracetam or piracetam with choline. This was not paired with placebos. Despite biochemical changes, there was no change in memory performance.

7. Nicholson CD *Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia*. Psychopharm 101:147-159, 1990. Review of literature to date on this topic. “Despite [piracetam’s] interesting animal pharmacology, convincing evidence that piracetam is an effective agent against the cognitive symptoms of primary dementia is still awaited....In
general, the trials have not been performed in well-defined patient collectives, but rather in patients with ill-defined psycho-organic brain syndromes.”


10. Weinstock M The pharmacology of Alzheimer’s Disease based on the cholinergic hypothesis: an update. Neurodegen 4: 349-356, 1995. A “where we are now” review of the literature, briefly touching upon piracetam as increasing alertness but without effect on memory or improving cognition.


**Piracetam and Myoclonus and other paroxysmal disorders**

(Note: myoclonus refers to the spasm or twitching of a muscle or group of muscles, and is not associated with a loss of consciousness. It can be a part of many neurologic diseases and can be cortical (epileptic) or subcortical. This appears to be the current main focus of attention of piracetam by UCB Pharma. “Paroxysmal” disorders are those with a sudden onset of a symptom, such as a seizure.)

1. Kunneke PS. A controlled clinical trial on the effect of piracetam in epileptic children. Br J Clin Practice 33(9): 266-271, 1979. 16 children with epilepsy and learning disorders given piracetam or placebo for 6 weeks. No effect on severity or frequency of
seizures noted. Researchers report a positive effect on visual perception and on memory as tested by digit spans.


4. Van Vleymen V and Van Zandijke M *Piracetam in the treatment of myoclonus: an overview*. Acta Neurol Belg 96: 270-280, 1996. This paper summarizes all trials and case reports known to the authors to date. It showed efficacy in several types of myoclonus, there was no obvious interaction with anticonvulsants, and adverse effects were rare.

5. Guerrini R et al. *Cortical myoclonus in Angelman syndrome*. Ann Neurol Jul;40(1):39-48, 1996. 11 patients with Angelman syndrome, ages 3 to 28 years. All had myoclonus with abnormal EEG activity. 5 were given piracetam, with good results for all five patients.

6. Dulac O et al. *Myoclonus and epilepsy in childhood: 1996 Royaumont meeting*. Epilepsy Research 30:91-106, 1998. This paper is a terrific resource for the description and etiology of all types of myoclonus. However, the portion dealing with treatment takes up only 2 full pages. Piracetam gets a brief mention: “In various types of cortical myoclonus including progressive myoclonic epilepsy and post anoxic myoclonus, it has marked effect on over one third of the cases...but is poorly effective against thalamocortical and subcortical myoclonus.”

7. Donma MM. *Clinical efficacy of piracetam in treatment of breath-holding spells*. Ped Neuro 18(1): 41-45, 1998. 39 children ages 6 to 36 months of age were given piracetam for 2 months, and
showed piracetam to be successful in stopping breath-holding spells from causing a loss of consciousness.

**Piracetam and Aphasia/Stroke**

1. Huber, W et al. *Piracetam as an adjuvant to language therapy for aphasia: a randomized double-blind placebo-controlled pilot study.* Arch Phys Med Rehabil 78: 245-250, 1997. 24 adults with stroke or brain injury resulting in moderate to severe aphasia were given piracetam along with speech therapy for 6 weeks. Piracetam had a significant effect on written language but not on spoken language. Total mean scores on an aphasia scale were higher with the group on piracetam.

2. De Deyn PP et al. *Treatment of acute ischemic stroke with piracetam.* Members of the Piracetam in Acute Stroke Study (PASS) Group. Stroke 28(12):2347-52, 1997. A multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients. Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Another study is underway decreasing the time interval to 7 hours.

**Piracetam and Blood Disorders**


2. Grekas D *A pilot study of piracetam in cuprophan hemodialysis.* Artificial Organs 13(5):422-426, 1989. Piracetam has an anti-platelet effect during blood-membrane interaction. (Note: this paper also references others I was unable to find that state
piracetam also has an anti-platelet effect in strokes and during transplants of kidneys and removal of spleens.)

3. Murayama M *Decompression-inducible platelet aggregation and hemostasis.* Thrombosis Research 54: 493-498, 1989. Texas Green frogs were used to study decompression effects on blood clotting. Frogs were exposed to the barometric pressure equivalent to the summit of Mt. Everest. Piracetam was found to block the platelet clumping normally produced by this type of decompression. (Note: this is my favorite study. Not only do they specify that this is the Texas green frog, but the best quote of all these papers is here: “Now it is generally known that there are great similarities between frog and man.” The only problem is, I do not know what a Texas green frog would be doing at the top of Mt. Everest.)


5. Moriau M et al. *Treatment of the Raynaud’s phenomenon with piracetam.* Arzneimittelforschung 43(5):526-35, 1993. A very nice paper in which piracetam was shown to be helpful in relieving the symptoms of Raynaud’s syndrome, probably through inhibition of platelet function and increasing red blood cell membrane deformability. Piracetam was well tolerated.


**Piracetam: Review Articles**

1. Gouliaev AH and Senning A *Piracetam and other structurally related nootropics.* Brain Res Rev, 1994; 19: 180-222. (This is an excellent review article. The section on piracetam by itself is only 6 pages, though.)
2. Vernon MW and Sorkin EM Piracetam: An overview of its pharmacological properties and a review of its therapeutic use in senile cognitive disorders. Drugs and Aging 1(1): 17-35, 1991. (Another excellent review article, and goes greatly into detail about its actions in the body as well as what is known about its use in presenile dementia.)


4. Mondadori C Nootropics: Preclinical results in the light of clinical effects; Comparison with tacrine. Critical Reviews in Neurobiology 10: 357-370, 1996. A review of clinical effects of nootropics in memory enhancement, and compared to tacrine, a cholinesterase inhibitor and the only drug registered to date in the US for Alzheimer’s disease. Mondadori, who has several studies published on piracetam, concludes: “Given the observed overall positive effects of the nootropics and their occasionally quite distinct effects in individual patients, this category of compounds would appear useful. The results available so far give no indication that tacrine is superior to the nootropics, or vice-versa.”

Piracetam (Nootropil) improves brain function and stimulates the central nervous system without any toxicity or addictive properties.

Piracetam is a member of the class of drugs known as nootropics or “smart drugs”. Nootropics are known commonly as cognitive enhancers, improving cognitive functions of the brain such as memory, attention and intelligence.

Piracetam also has a beneficial effect upon the brain’s Corpus Callosum. This is the area of the brain that joins the two
hemispheres, linking the logical side of the brain with the creative side of the brain, allowing the user to draw on greater brain potential.

Piracetam has been used successfully to treat alcoholism and alcohol withdrawal syndrome in animals and man. It has brought improvement, or slowed deterioration, in ‘senile involution’ dementia and Alzheimer’s disease. Piracetam has improved recovery from aphasia (speech impairment) after stroke, and restored various functions (use of limbs, speech, EEG, state of consciousness) in people suffering from acute and chronic cerebral ischaemia (decreased brain blood flow). Piracetam has improved alertness, cooperation, socialisation and IQ in elderly psychiatric patients suffering from ‘mild diffuse cerebral impairment.’

Piracetam has increased reading comprehension and accuracy in dyslexic children. It increased memory and verbal learning in dyslexic children, as well as speed and accuracy of reading, writing and spelling. Piracetam potentiated the anticonvulsant action of various anti-epileptic drugs in both animals and man, while also eliminating cognitive deficits induced by anti-epileptic drugs in humans. It has improved mental performance in ‘aging, non-deteriorated individuals’ suffering only from ‘middle-aged forgetfulness’. Elderly out-patients suffering from ‘age-associated memory impairment’ given Piracetam showed significant improvement in memory consolidation and recall. Piracetam reversed typical EEG slowing associated with ‘normal’ and pathological human aging, increasing alpha and beta (fast) EEG activity and reducing delta and theta (slow) EEG activity, while simultaneously increasing vigilance, attention and memory.

The effect of Piracetam can be increased if taken with DMAE, Centrophenoxine, Choline or Hydergine. When Choline and Piracetam are taken together there is a synergistic effect that causes a greater improvement in memory than the sum of each when taken alone.
Dosage:
A common starting dose is three 800mg tablets twice a day, lowering to one or two tablets twice a day after a month.

Caution:
Remember that all nootropics are synergistic with each other and with other brain nutrition products (such as, Choline, DMAE, Hydergine and Centrophenoxine). When combining these products, the individual doses may have to be reduced in order to avoid possible side effects of nausea and headaches.