The Piracetam-nootropics (pyrrolidone derivatives) have been exhaustively researched for more than three decades. Experimental and clinical work first focused on their so-called nootropic effects; later came the possibilities for neuroprotection after stroke and use as antiepileptic agents. The concept and definition of a “nootropic drug” was first proposed in 1972 by C.E. Guirgea, the principal Piracetam researcher for UCB Pharmaceutical Company of Belgium that launched Piracetam. He coined the term "nootropic" from the italic words "noos" (mind) and "tropein" (to turn toward), to mean enhancement of learning and memory.

The main features defining a nootropic drug are:

1. **The enhancement of learning and memory acquisitions as well as resistance of learned behaviours to agents that tend to impair them.**
2. **Protection of brain against various physical or chemical injuries.**
3. **Facilitation of interhemispheric flow of information and efficient tonic cortical/subcortical mechanism.**
4. **Absence of the usual negative pharmacologic effects of psychotropic drugs.**

Piracetam was the first nootropic agent discovered and has been licensed in many countries like India, Belgium, Austria, Germany, and Switzerland for its antiamyoclonic action, effects after stroke and in mild cognitive impairment. Levetiracetam was registered for epilepsy in 1999 and has been licensed in USA, Switzerland, Argentina and Norway for its use in epilepsy. The other nootropics agents- Aniracetam, Fosracetam, Nefiracetan, Pramiracetam, Nebracetam and Oxiracetam are in various stages of licensing and investigation. A notable feature of this drug is the relative lack of adverse effects (especially CNS toxicity), which contrasts with other psychotropic drug classes (e.g., the NMDA [N-methyl D-aspartate] antagonists) which have been investigated in the same general therapeutic areas. They are toxicologically the safest drugs ever developed.

**Pharmacological properties of nootropics:** Extensive study of the modes of action of the nootropics has revealed various pharmacological effects. There may be no single predominant mode of action that is shared by the whole drug class. All these drugs however influence cholinergic function. By increasing high affinity choline uptake these drugs facilitate acetylcholine production and turnover with varying actions at both muscarinic and nicotinic receptors.

There is a serious decline in acetylcholine receptors in normal aging in humans. Piracetam elevates the density of frontal cortex acetylcholine receptors by 30-40% restoring the levels of acetylcholine in the brain.

Energy (ATP) is critical to the brain’s very survival and brain cells must produce all their own ATP from glucose (sugar) and oxygen. They cannot borrow ATP from other cells. Brain carbohydrate metabolism is impaired in a variety of dementias and the degree of reduction in brain carbohydrate metabolism correlated with the severity of the dementia. Piracetam increases the activity of adenylate kinase enzyme that converts ADP into ATP and AMP. This reduces the drop in ATP in oxygen-compromised brain. Thus, it prevents the dementia and speeds up the recovery from hypoxia due to enhancement of oxidative glycolysis.

It increases cerebral blood flow, cerebral oxygen usage metabolic rate and cerebral glucose metabolic rate in chronic impaired human brain function i.e., multi-infarct (stroke) dementia, senile dementia of the Alzheimer type and pseudo dementia, ischaemic cerebral (poor brain blood flow) infarcts. It reduces the platelet aggregation and has haemorrhheological and antithrombotic effects. It also changes the physical properties of membranes, and enhances membrane fluidity, presumably by binding to membrane phospholipids. It improves erythrocyte function, decreases the adherence of damaged and sickle cell red blood cells to the endothelium, increases prostacyclin (PGI₂) production and activity, enhances phospholipids - metabolism and protein biosynthesis.

It increases synthesis and turnover of cytochrome b5, a key component of the electron transport chain, wherein most ATP energy is produced in mitochondria and increases permeability of mitochondrial membranes for certain intermediaries of the Krebs cycle. It enhances transcomisural encoding mechanisms and some form of inter-hemispheric/intercerebral transfer.
Levetiracetam, an antiepileptic agent acts by reducing high-voltage activated calcium conductance, and its action has been postulated to modulate intracellular calcium buffering and transport mechanisms. It reverses the inhibition of negative allosteric modulators of both GABA and glycine gated currents. It also holds the promise in the field of neuroprotection.

Nefiracetam also has strong antiepileptic effects but by different unknown mechanism.

Pramiracetam has been shown to increase nitric oxide synthase activity. It is licensed in Italy as a cognitive enhancer.

Fosiracetam causes up-regulation of the GABA receptor, stimulates cAMP formation, and shows striking positive effects in spatial memory tests in ischaemic state. It is currently in phase III trials in Alzheimer's disease and in cerebrovascular disease. A striking feature of all these drugs is their stereospecificity; minor changes in structure resulting in remarkable differences in pharmacological activity. A good example is the strong cerebral binding and antiepileptic properties of Levetiracetam, which is the S-enantiomer; the R-enantiomer is inactive. Studies of the pharmacokinetics of nootropics indicate that these drugs have favorable properties for acute and chronic oral use.

**Indications:** Piracetam: post stroke, cognitive impairment, organic brain syndrome, multi-infarct dementia, senile dementia, Alzheimer's disease, post concussional syndrome, post traumatic vertigo and coma, dyslexia, aphasia, alcoholism, alcohol withdrawal, head injury, sickle cell anemia, Raynaud's disease, Parkinson's disease, post anoxic myoclonus, primary generalised epilepsy with myoclonus, hypoxia, anoxia, cerebrovascular insufficiency. Levetiracetam: epilepsy, myoclonus.

Other nootropic agents in this class are currently at an advance stage of development and will enter clinical practice in the next few years and clinical indications of drugs already licensed will also widen.

**Sources:** www.about.com

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**SCHIZOPHRENIA DRUGS INCREASE RISK OF CARDIAC ARREST**

Patients with schizophrenia who take antipsychotic drugs are more likely to have a cardiac arrest than non-schizophrenic patients, finds a study in BMJ.

Using data from three US Medicaid programmes, researchers compared the frequency of cardiac events among patients with treated schizophrenia and control patients with psoriasis or glaucoma. They also compared the cardiac risk of different antipsychotic drugs (thioridazine, haloperidol, risperidone, and clozapine).

They found that patients with treated schizophrenia had higher rates of cardiac events than controls.

Overall, the risk with thioridazine was no worse than that with haloperidol. Thioridazine may carry a greater risk than haloperidol at high doses, although this finding could be due to chance, say the authors.

To reduce cardiac risk, patients requiring thioridazine should be treated with the lowest dose possible to treat their symptoms, they conclude.

*(Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data - http://bmj.com/cgi/content/full/325/7372/1070)*