Nootropics in the Classification of Psychotropics: Therapeutic Implications

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Introduction

The term "nootropics", was proposed by Giurgea in 1972 for a new class of psychotropic drugs with selective activity on the "higher integrative mechanisms of the brain". To explain the distinctiveness of nootropics from other psychotropic drugs, he suggested that "nootropics" exert their action at the level of the telencepalon exclusively (Giurgea, 1976).

Instrumental to the development of the "nootropic concept" was the synthesis of piracetam, a 2-oxo-pyrrolidine acetamide, and the demonstration that piracetam, in normal subjects, improved ("activated") the efficiency of higher nervous functions, while in patients with brain injury, "facilitated the restoration" of normal brain activity (Giurgea 1981). Since the "facilitation of restoration" was independent from the etiology of the injury, he raised the possibility that piracetam, and piracetam–like "nootropics", might have a place in the treatment of organic, including old age dementias.

In the following the conceptual development of currently used classifications of psychotropic drugs with special reference to the class of "nootropics" will be reviewed, and the conceptual development of currently used classifications of psychiatric disorders, with special reference to the organic dementias will be outlined. Within this frame of reference, therapeutic implications of nootropics will be discussed.

Classification of Psychotropic Drugs

The term "psychotropics" was proposed by Gerard in 1957 for a new class of CNS acting drugs with the common characteristic of "psychic tropism", expressed by effects on mental and emotional processes. In contradistinction to traditional stimulants and sedatives, it was suggested, that psychotropics selectively induce (psychotopathics or psychomimetics) or correct (psychotherapeutics) pathological conscious experiences (Ban, 1969).

Introduction of the "psychotropic concept" led to a re-valuation of the classification of central nervous system acting drugs. It was the result of this re-evaluation that Jean Delay, in the late 1950s, divided psychotropic drugs into "psycholeptics", "psychoanaleptics", and "psychodyleptics", corresponding to some extent with the traditional categories of "sedatives", "stimulants", and "psychomimetics". Furthermore, to provide a lead for the clinical use of new drugs, he suggested to distinguish within "psycholeptics", between "depressors of vigilance", i.e., "hypnotics", and "depressors of affect", i.e., "tranquilizers", and within "psychoanaleptics", between "stimulants of vigilance", i.e., "psychostimulants" and "stimulants of affect", i.e,."antidepressants".

The classification of "psychotropics", was further refined in the early 1960s by Heinz Lehmann, who suggested to distinguish within "depressors of affect", between "anxiolytic tranquilizers" with a potential to relieve tension and anxiety, and "antipsychotic neuroleptics" with a potential to control psychotic symptoms. After Lehmann's refinement, about ten years passed before, in 1977, Giurgea

suggested to include in the psychoanaleptic class a new group of drugs, he referred to as "nootropics". Accordingly, in Giurgea's (1981) classification, psychoanaleptics were separated into "behavioral activators", i.e., "psyychostimulants", "mood activators", i.e., "antidepressants", and "noetic activators", i.e., "nootropics".

Classification of Psychiatric Disorders

Functional vs. Organic Syndromes

By adopting the basic rules eployed byLinne (1825) for the clasiication of flowering plants, Boisser de Sauvages (1768) made an attempt in 1768 to classify mental illness. It was the strong influence of his nosology on French psychiatry, that led to the classification of Pinel, whose taxonomy consisted of "empirically isolated syndromic classes" (Pichot, 1986).

Pinel distributed the different "mental derangements" into five "different species" of disease, and adopted the term, "dementia" or the "abolition of the thinking faculty" fort the fourth species.

Similar to Pinel (1806), Esquirol (1845) separated the "general forms of insanity" into five variety and used the term "dementia" four the fourth variety in which "the insensate utter folly, because the organs of thought have lost their energy and the strength requisite to fulfill their functions".

Probably the single most important contribution to the conceptual development of diagnostic classifications in psychiatry was the work of Bayle (1826) who was the first to note that a chronic neuropathologic process, chronic arachnoiditis resulted in "dementia" in the terminal stage of its development. Bayle's (1826) work opened the path for the recognition that other diseases, which are based on an identifiable neuropathologic process, such as Huntington's (1872) chorea, Pick's (1892) disease, Alzheimer's (~~1970~~ 1907) disease and Jakob (1920) and Creutzfeldt's (1921) disease all lead to dementia in the terminal stage of their development. It also provided the necessary reference points for Morel (1852), Lasegue (1852), Falret (1854) and Magnan (1893) for the separation of the major functional psychiatric syndromes from organic dementia.

From the point of view of clinical psychopathology, the essential difference between functional (or primary) and organic (or secondary) psychiatric syndromes is in the developmental pattern of the clinical-psychiatric manifestations, i.e., increasing differentiation of psychopathologic structures in the functional syndromes, and dedifferentiation in the organic-dementia syndrome. Accordingly, in the course of increasing differentiation, each functional syndrome develops into a number of distinct disease forms and subforms, whereas in the course of increasing dedifferentiation, different organic disorders are merged into one and the same chronic-dementia syndrome.

In favor of the contention that dementia is the result of increasing dedifferentiation of psychopathologic structures, were the observations of Jaspers (1910). He noted a "haphazard" variety of psychopathologic manifestations in patients with dementing disorders at an early stage of their illness; and the gradual replacement of these colorful early manifestations by

chronic-dementia with the progress of the neuropathologic process in all the different illnesses. In keeping with this, and the non-specific nature of the dementia syndrome, is that at least ten different classes of disorders--degenerative, vascular, myelinoclastic, traumatic, neoplastic, hydrocephalic, inflammatory, infection related, toxic and metabolic--have been encountered in patients with organic-dementia (Cummings, 1987).

The non-specific nature of the dementia syndrome raises the possibility that nootropics might be useful, even if they are not causal treatments, in a wide variety of diseases, subsumed under organic dementia.

Dementia Syndrome

There is considerable agreement regarding diagnostic criteria of the dementia syndrome between the two prevalent systems of diagnostic classifications, i.e., DSM-III-R and ICD-10 Draft. The primary requirement in both is the simultaneous decline in both memory and thinking in a sufficient degree to impair functioning in daily living, i.e., work, usual social activities and/or relationships with others. In both systems, the ultimate diagnosis of dementia can only be made when consciousness is clear; and the ICD-10 Draft maintains that for a "confident diagnosis" the pivotal symptoms and impairments need to be "in evidence for at least six months."

Recently, on the basis of research in progressive supranuclear palsy (Albert, Feldman and Willis, 1974) and in Huntington's chorea (McHugh and Folstein, 1975), it was suggested, that dementia, as a syndromic diagnosis, consists of two distinct forms, one referred to as "cortical dementia" and the other as "subcortical dementia" (Cummings and 8enson, 1984). Proponents of this separation maintain that in cortical dementia, the prototypes of which are Alzheimer's disease and Pick's disease, the primary changes are in the

cerbral cortex and the prevailing clinical manifestations are instrumental deficits, such as aphasia, amnesia, apraxia, agnosia and constructional difficulties; whereas in subcortical dementia, the prototypes of which are Parkinson's disease, Huntington's chorea, progressive supranuclear palsy, spinocerebeller degeneration, idiopathic basal ganglia classification, striatonigral degeneration, Wilson's disease and thalamic dementia, the primary changes are in subcortical structures and the prevailing manifestations are psychomotor retardation, apathy, lack of initiative and decreased spontaneity. In spite of the great heuristic implications of this line of research, however, Mayeux and his associates (1983) were unable to detect significant differences by neuropsychological testing between patients with cortical dementia, such as Alzheimer's disease, and subcortical dementia, such as Parkinson's disease and Huntington's chorea. Similarly, Benson (1984) found that patients with Parkinson's disease and Huntington's chorea frequently displayed the clinical manifestations of both cortical and subcortical dementia (Tariska, 1986). The same applies to multi-infarct dementia (Frederiks, 1985). This might explain why in the differentiation of primary degenerative (senile) dementia of the Alzheimer type (SDAT) and multi-infarct dementia (MID) neither cross-sectional psychopathology, nor therapeutic responsiveness to nootropics suffice. It might also explain the lack of clear-cut difference in performance changes to pharmacological load tests between the two major late onset dementia (Lehmann and Ban, 1970).

Pharmacotherapy of Organic Dementia

Causal Treatments

Pharmacotherapy of dementia is intrinsically linked to the understanding that dementia is a syndrome and not an illness. Since the presence of

dementia indicates a systemic, including neurologic or toxic disease, identification of the causal factor may lead to rational treatment. Introduction of rational treatment led to the virtual elimination dementia in patients with pellagra, i.e., nicotinic acid deficiency, and in patients with cerebral syphilis. If one considers that at the beginning of the century 10 percent of all psychiatric beds were occupied by patients with general paralysis, i.e., by patients with dementia resulting from cerebral syphilis, while today this figure is well below 1 percent, one has to accept that one of the greatest successes of modern medicine has been in the treatment of organic dementia.

Heuristic Treatments

Current investigational treatments are primarily based on hypotheses generated by neurochemical findings in the brains of SDAT patients and not on etiologic considerations. Such findings include the loss of neurons in the basal forebrain cholinergic system, in the noradrenergic locus coeruleus and in the serotoninergic raphe nuclei; and severe neuronal deficits in the amygdala, hippocampus and neocortex with a decrease in the level of somatostatin, gamma-aminobutyric acid, aspartate and corticotropin. Nevertheless, despite the consistent loss of presynaptic cholinergic markers, the pattern of change in cortical muscarinic receptors has remained unclear (Whitehouse, 1987).

On the basis of these findings numerous clinical trials were designed and carried out in a limited number of patients. Included among them were studies with acetylcholine precursors, such as choline and lecithin, with anticholinesterases, such as physostigmine and tetrahydraaminoacridine, and with the cholinergic agonist, bethanechol. Included also were studies with opoid antagonists, such as naloxone and naltrexone, and with the octopeptide, vasopressin (Dysken, 1987).

Treatment with Nootropics

There are also several nootropic drugs in clinical use/investigation in Europe, e.g., pyritinol, oxiracetam. Among them, the most extensively studied is piracetam, the prototype of nootropics which in 9 out of 14 clinical studies (12 conducted in patients with "senile involution", and two in patients with "dementia"), was found to produce statistically significantly greater improvement in cognitive functioning than an inactive placebo.

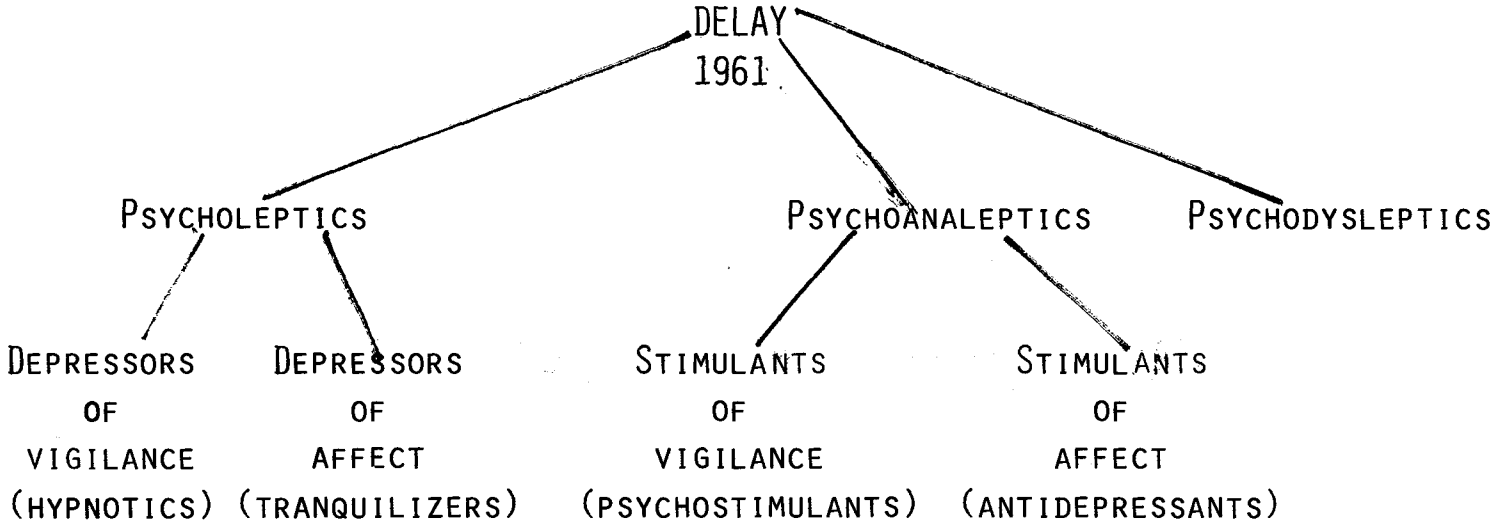
Conclusions

In the foregoing nootropics were characterized as drugs which activate higher nervous functions in normal subjects and facilitate restoration of normal brain activity in brain injury, regardless of its nature. They were classified as "psychoanaleptics" that "activate noetic activity". It was pointed out that "dementia" is not an illness, but a syndrome that develops as a result of de-differentiation of psychopathologic structures in several neuropsychiatric disorders. The possibility was raised that treatment with piracetam may have a place in the in the treatment of dementia.

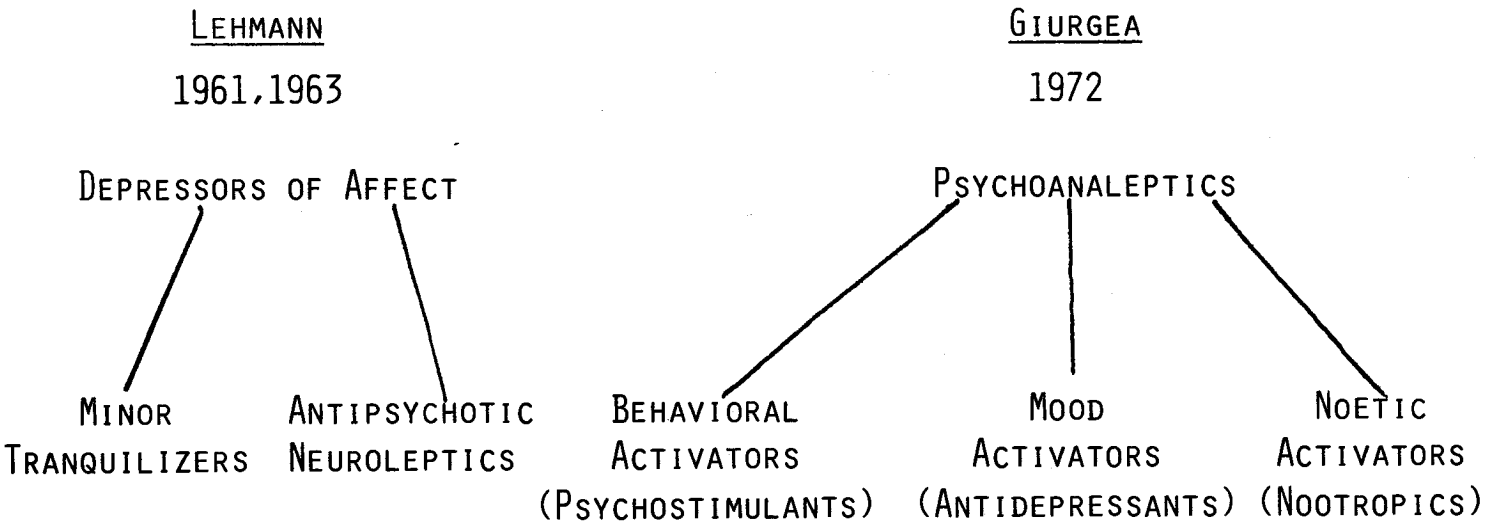
References

Giurgea C. Vers une pharmacologie de l'activite integrative du cerveau. Tentative du concept nootrope en psychopharmacologie. *Actualites pharmacologiques* 25eme serie, p.115 a 156 1972)(

TABLE


DELAY
1961
PSYCHOLEPTICS
PSYCHOANALEPTICS
PSYCHODYSLEPTICS
DEPRESSORS OF VIGILANCE (HYPNOTICS)
DEPRESSORS OF AFFECT (TRANQUILIZERS)
STIMULANTS OF VIGILANCE (PSYCHOSTIMULANTS)
STIMULANTS OF AFFECT (ANTIDEPRESSANTS)

TABLE


LEHMANN
1961,1963
DEPRESSORS OF AFFECT
MINOR TRANQUILIZERS
ANTIPSYCHOTIC NEUROLEPTICS
GIURGEA
1972
PSYCHOANALEPTICS
BEHAVIORAL ACTIVATORS (PSYCHOSTIMULANTS)
MOOD ACTIVATORS (ANTIDEPRESSANTS)
NOETIC ACTIVATORS (NOOTROPICS)

TABLE

NOOTROPICS

14 DOUBLE-BLIND PLACEBO-CONTROLLED STUDIES

SIGNIFICANTLY GREATER IMPROVEMENT WITH PIRACETAM THAN PLACEBO

COGNITIVE IMPAIRMENT	9 STUDIES
GLOBAL EVALUATION	7 STUDIES