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PAST AND FUTURE OF NEUROPSYCHOPHARMACOLOGY

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Summary. - *The advent of what is called the chemotherapy of mental diseases goes back to the early fifties, when a series of clinical observations led medical research to reconsider this field, that at the time was not particularly developed. The use of chlorpromazine and of reserpine in the therapy of some psychotic syndromes dates back to that time. A few years later meprobamate was introduced and proved active against anxiety. The success obtained with these drugs was followed by a flourishing of research carried out in a joint effort by pharmacologists and clinicians. This cooperation gave birth to a new discipline, the neuropsychopharmacology. In the course of time, through a progressive refining of the techniques it has been possible to acquire methods particularly suitable for the identification of the effects of the various drugs acting on the CNS. If the sixties were the decade of the synapse, during the seventies the main interest of research was focused on receptors, and the eighties can be considered the decade of post-receptor intraneuronal mechanisms. As far as the future of research is concerned, priority must be given to scientific approaches that:* a) *explore in a new and original chemistry;* b) *use advanced pharmacological techniques;* c) *start from scientific hypotheses based on recent discoveries and if possible suggested by scientists. Recently, special attention has been devoted to the study of inhibitors of proteolitic enzymes responsible for the degradation of enkephalins which allegedly should reinforce the endogenous mechanisms for the control of pain. Encouraging data are already available but these preliminary results should be confirmed before going into more extended investigations. The second topic concerns the peptides. As a consequence of the development of the chemistry of peptides and of the study of their effects and their mechanisms of action, we have witnessed one of the most interesting evolution of neurobiological research. One has realised, in fact, that many of the drugs used until now are non peptidic peptido-mimetics. If this new trend will be followed, the old drugs will be substituted by new ones having a peptidic or semipeptidic structure. Third and last topic is the pharmacological therapy aiming at the improvement on the quality of life of old people. The efforts made by pharmacologists for a good evaluation of the effects of a drug in the laboratory are useless if they are not followed by a proper research in man. The problem, therefore, is to be solved by clinicians, to whom we must give all the possible help coming from basic research. From our investigations, for instance, it appears that the functional deficit in chronic cerebral syndromes has multi-faceted aspects. The therapeutic strategy will be therefore that of multiple pharmacological interventions to tackle the complex components of this disease.*

Riassunto (Passato e futuro della neuropsicofarmacologia). - *L'avvento della cosiddetta chemioterapia delle malattie mentali risale all'inizio degli anni '50, allorché una serie di osservazioni cliniche indusse i ricercatori a rivolgere la loro attenzione a questo particolare problema, fino ad allora scarsamente sentito. Risale a quel tempo l'introduzione della clorpromazina e della reserpina nella terapia di alcune sindromi psicotiche. Successivamente fu la volta del meprobamato, per il quale venne evidenziata l'efficacia terapeutica negli stati ansiosi. Il fiorire delle ricerche che seguì i buoni risultati ottenuti con questi farmaci fu caratterizzato dalla stretta collaborazione tra farmacologi e clinici. Questa collaborazione segnò la nascita di una nuova disciplina, la neuropsicofarmacologia. Nel corso degli anni, attraverso il progressivo affinamento delle tecniche, sono stati messi a punto metodi sempre più adatti a riconoscere in laboratorio gli effetti di uno psicofarmaco. Se gli anni '60 furono la decade della sinapsi, gli studi degli anni '70 si sono concentrati sui recettori, negli anni '80 sono invece i meccanismi intraneuronali a richiamare l'attenzione dei ricercatori. Per quello che riguarda le future ricerche, dovranno avere la priorità gli approcci scientifici che:* a) *esplorano in una chimica nuova ed originale;* b) *si avvalgono di metodologie farmacologiche avanzate;* c) *partono da presupposti scientifici frutto di scoperte recenti e possibilmente ispirati dai ricercatori. In particolare,*

l'attenzione dei ricercatori si è rivolta recentemente allo studio di inibitori degli enzimi proteolitici preposti alla degradazione delle endorfine e delle enkefaline, e che dovrebbero permettere un rafforzamento del sistema endogeno di controllo del dolore. I primi incoraggianti risultati si incominciano ad avere, ma queste ipotesi richiedono, evidentemente, ulteriori conferme sperimentali prima di essere del tutto accettate. Una seconda linea di ricerca riguarda i peptidi. Grazie allo sviluppo della chimica dei peptidi e allo studio dei loro effetti e del loro meccanismo di azione, in questi ultimi anni abbiamo assistito a uno dei fenomeni concettualmente più interessanti della ricerca in questo campo. Ci si è resi conto infatti che molti dei farmaci che abbiamo usato finora sono dei peptidomimetici non peptidici e che la attuale strategia ci porterà a sostituire i vecchi farmaci con dei nuovi a struttura peptidica o emipeptidica. Il terzo e ultimo punto è quello degli interventi farmacologici volti a migliorare la qualità della vita dell'anziano. Certamente, indagini di questo genere presentano una serie di problemi e limitazioni metodologiche, ma noi tutti sappiamo che sono stati messi a punto programmi di ricerca sull'uomo il cui rigore scientifico non è in discussione. La soluzione di questo problema è pertanto nelle mani dei clinici, a cui noi dobbiamo dare tutto il possibile supporto che può provenire dalle ricerche di base. Da queste ricerche, per esempio, è emerso che la sofferenza cerebrale cronica ha un carattere composito. La strategia terapeutica che ne deriva è quella di interventi farmacologici multipli, che tengano conto della complessità dei deficit della organizzazione neuronale dell'anziano.

When organizing this seventh Italo-Soviet meeting I received the suggestion by some of our colleagues to prepare a short history of neuropsychopharmacology. I consider therefore the best welcome to our Soviet and Italian friends to remember and comment the various stages of a discipline to which all of us have devoted most of our time. In this connection, I must say that it has been very rewarding, during the preparation of this conference, to recall and record the remarkable developments that have occurred during these years and in which I participated.

The advent of what is called the chemotherapy of mental diseases goes back to the early fifties, when a series of clinical observations led medical research to reconsider this field, that at the time was not particularly developed. The use of chlorpromazine and of reserpine in the therapy of some psychotic syndromes dates back to that time. A few years later meprobamate was introduced and proved active against anxiety.

The success obtained with these drugs was followed by a flourishing of research carried out in a joint effort by pharmacologists and clinicians. This cooperation gave birth to a new discipline, the neuropsychopharmacology. After many years of intense activity, a period of evaluation of the studies

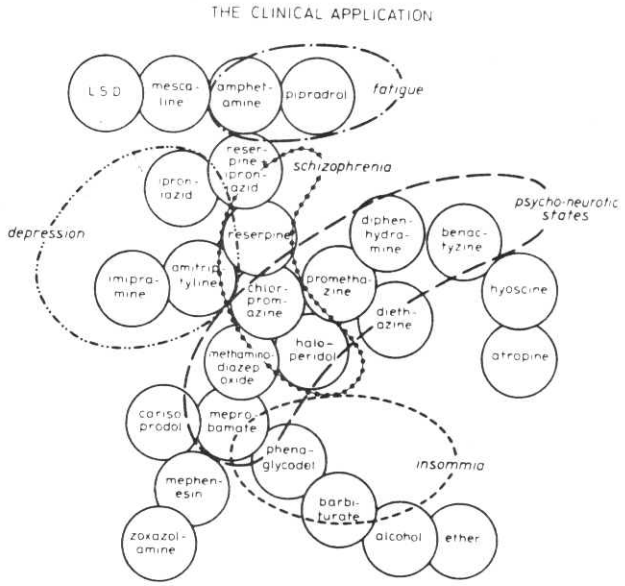

Fig. 1. - This diagram is redrawn from a paper published by Jacobsen (*Clin. Pharmacol.* 4: 480, 1963). On the basis of the data available at that time, some psychotropic drugs are grouped according to various types of action. Note that many compounds present in the diagram are not in use today; note also the first common name given to chlordiazepoxide (methaminodiazepoxide).

carried out in the field followed. A large number of meetings and symposia were organized with the purpose of classifying these new drugs and to compare their effects in man with those obtained in laboratory animals (Fig. 1). The establishment of previsional pharmacology in this field can therefore be dated back to the late fifties.

In the course of time, through a progressive refining of the techniques it has been possible to acquire methods particularly suitable for the identification of the effects of the various drugs acting on the CNS. If the sixties were the decade of the synapse, during the seventies the main interest of research was focused on receptors, and the eighties can be considered the decade of post-receptor intraneuronal mechanisms.

Unfortunately, previsional pharmacology in the field of neuro- and psychotropic drugs was not as satisfactory as in other fields. After years of research more than one theory on the mechanism of action of some psychotropic drugs proved to be wrong. For instance, at first a great importance was given to the effect of tricyclic antidepressants on the uptake of neurotransmitters, but a reevaluation of available data brought up the much more significant relevance of their long-term effects on serotonin and noradrenaline receptors and, more recently, of their short- and long-term effects on $GABA_B$ receptors [1].

We must be grateful therefore to some enlightened researchers, who took the initiative to try clinically compounds that, although not having the classical action of tricyclic antidepressants on uptake, yet showed similar effects on some tests of behavioural pharmacology. It is indisputable that today a number of antidepressants used in clinic are «atypical»

Table 1. - *Classification of psychotropic drugs*

Psycholeptics:	
Sedative	Barbiturates Chloral hydrate Derivates Alcohol
Antipsychotics or neuroleptics	Phenotiazines Butyrophenones Tioxantenes Reserpine Atypical (pimozide, sulpiride)
Anxiolytics	Benzodiazepines Non benzodiazepine derivates (zolpidem, suriclone) Atypical (buspirone, ketanserin)
Mood regulators	Lithium
Psychoanaleptics:	
Stimulants	Amphetamine, caffeine, cocaine
Antidepressives thymeretics	Mao inhibitors
Antidepressives thymoleptics	Tricyclics (amitriptiline, imipramine) Atypical (mianserine, trazodone, viloxazine)
Nootropics	Piracetam, piritinole, hydergine, nicergoline
Psychodysleptics:	
Hallucinogenics	Indolanchilamines (LSD, psylocibine) β -phenylethylamines (mescaline, dimethoxyamphetamine, phenciclidine
Opiates	Morphine, heroin

and yet have a therapeutical effect which is by no means lesser than that displayed by the «classical» products (Table 1). On this basis a question arises: how many potentially useful drugs have been discarded because they did not conform to the profile of action rigidly established in early times? The discovery of the existence in the brain of specific sites where some neurotropic and psychotropic drugs bind, dates back to the seventies (the receptors era). Allegedly, it is at the level of these sites that the drugs begin their therapeutical effect. As a consequence, *in vitro* investigations in order to test the capacity of a new product of binding on a specific site entered in widespread use, comparing the new drug with those already known to be active in this field. This method, of relatively simple execution, is still adopted in the first phase of the screening of new products.

The whole idea of the «receptors» gave new impulse to the definition of the mechanism of action of psychotropic drugs and to research on the etiopathogenesis of mental diseases. The hypothesis «if there is

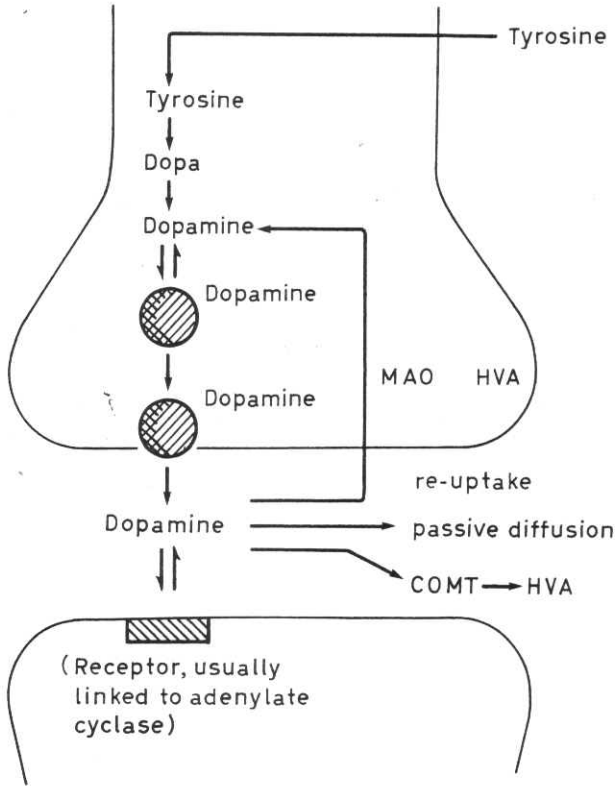

Fig. 2. - Synthesis, release and inactivation at the level of the synapse of a « classical» neurotransmitter, dopamine.

a receptor there must be also its endogenous ligand» has stimulated the interest of neurobiologists.

Our present knowledge on the binding sites for neuro- and psychotropic drugs can be grouped along three levels:

1) receptors *stricto sensu*, for which are known both the endogenous ligands (neurotransmitters, modulators) that are the target of psychotropic drugs, and the transduction mechanisms that follow the binding to the receptors (Fig. 2);

2) the so called «pharmacological receptors» whose endogenous ligands and/or mechanisms of transduction are not yet completely known (Fig. 3);

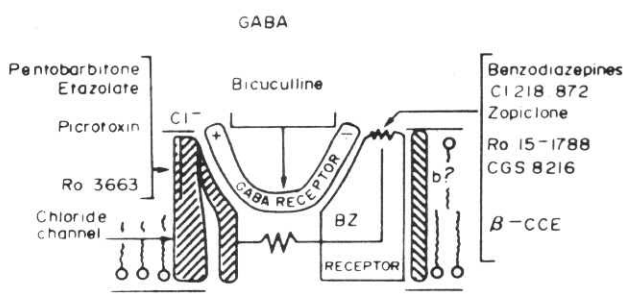

Fig. 3. - Suggested model of the receptor to GABA-benzodiazepine-chloride channel. The channel is activated both by the GABA-agonist drugs and the barbiturates, while is blocked by the convulsants. The benzodiazepines allegedly act through a «modulation» of the GABA receptors.

3) the so called «pharmacological acceptors» [2] whose endogenous ligands and/or transductors are still the object of study since an acceptable hypothesis has not yet been formulated.

The discovery and the progress made in the field of receptors and of their endogenous ligands [3] has allowed a more rational planning of the research on neuro- and psychotropic drugs. The following examples are particularly significant.

The opiates [4] have recently attracted the attention of pharmacologists not only for their effects on pain [5] but also because of their influence on other cerebral activities. I shall treat this subject later.

The second example is that of the anxiolytic drugs. Starting from the discovery of the benzodiazepine receptor, we have witnessed in this field an evolution which will probably render obsolete the benzodiazepine class [6]. As a matter of fact, the introduction in therapy of drugs with a structure and mechanism of action distinct or different from that of the benzodiazepine derivatives, has strengthened the hypothesis that anxiety disorders may be dependent upon a multiplicity of mechanisms (Table 2 and Fig. 3). It is very interesting in this regard the slow lytic effect on anxiety described after some drugs such as buspirone, opposed to the anxiolysis by crisis that is obtained with benzodiazepines [7].

The third example concerns the drugs that are able to act on depression. For these drugs I anticipate that the discovery of specific receptors for the tricyclics [8] and the connected research on the existence of one or more endogenous substances, will bring to an end the era of the tricyclic antidepressants.

Neuropsychopharmacological research has largely used the methods of experimental psychology. Undoubtedly, these techniques still have an important place in preclinical research, and often they have contributed in outlining the pharmacodynamic effects of a psychotropic drug. However, looking back critically to the many years spent in this kind of research, it is doubtful whether behavioural studies, in contrast to biochemical studies, have greatly advanced our understanding of the mechanism of action of psychotropic drugs. This is easy to explain if one considers that behavioural regulation on one side and the effects of a drug on the other, are processes of such a complexity that their reciprocal interaction could not give enligthening results.

Table 2. - *Non-benzodiazepine anxiolytics*

Affinity for BDZ receptor	**Effects on other neurotransmitters**
Zopiclone	Buspirone (DA, 5HT)
Suriclone	Ketanserine (5HT)
CL 218872	Ipsapirone (5HT)
CGS 8216	Gepirone (5HT)
Cartazolate	
Tracazolate	
Alpidem	
Zolpidem	

I would like now to speak of my personal views on the future of research in this field. If we want to be realistic we must first of all admit that the research of the next years will have its roots in the work that we are doing today, in accordance to the well known motto which says: «future has already begun».

Obviously, priority must be given to scientific approaches that: *a*) explore in a new and original chemistry; *b*) use advanced pharmacological techniques; *c*) start from scientific hypotheses based on recent discoveries and if possible suggested by scientists. Research aiming at small variations of drugs already used in therapy undoubtedly is easier, but actually it will lead only to products of limited novelty and therefore difficult to introduce into clinical use. Therefore the best approach, also from an economical point of view, is to keep in mind that the success of research depends upon finding drugs that, because of their innovative character, will be easily accepted in the market.

In the rest of the time at my disposal, I would like to outline now some field of research that I consider worth developing.

A linè of research that could give results of high relevance both from a theoretical and practical point of view, concerns the field of analgesic drugs. The discovery of enkephalin and of endorphin and of their important role in analgesia has led to the synthesis of a great number of analogues with pain obtunding properties even stronger than that of the classical opiate products. Nevertheless, these new drugs offer no particular advantage for what concerns the side-effects of opiates, such as respiratory depression or addiction.

Studies carried out to establish the presence of enkephalins and endorphins in various regions of the central nervous system have shown the mechanism of release and destruction of these substances. Recently, special attention has been devoted to the study of inhibitors of the proteolytic enzymes responsible for the degradation of enkephalins, which allegedly should reinforce the endogenous mechanisms for the control of pain. Encouraging data are already available but these preliminary results should be confirmed before going into more extended investigations [9].

The second topic that I have chosen concerns the peptides. To illustrate the rapid advancement in this field it is sufficient to point out that the chapter concerning the peptides in the 1970 edition of Burger's Medicinal Chemistry covered 13 pages, while in the 1980 edition 129 pages are dedicated to the subject. As a consequence of the development of the chemistry of peptides and of the study of their

effects and their mechanisms of action, we have witnessed one of the most interesting evolution of neurobiological research. One has realised, in fact, that many of the drugs used until now are, as Ariens says [10], non peptidic peptido-mimetics. If this new trend will be followed, the old drugs will be substituted by new ones having a peptidic or emipeptidic structure. But also today there are some pharmacological categories, such as the opioids, some pituitary hormones, the hypotalamic releasing factors, in which the strategy for the development of peptide drugs has led to major successes. The examples given are the best demostration that if one assembles a team of organic chemists, pharmacologists and clinicians, who are willing to work closely together, peptide research can be a fruitful area for the development of novel psychotropic drugs (Fig. 4). And for a not too remote future one may easily predict that the actual peptidomimetic non peptidic antipsychotics will be substituted with peptides, and that new peptides will take the place of today's tranquillizers and antidepressants.

Third and last topic is the pharmacological therapy aiming at the improvement of the quality of life of old people. There seems to exist a curious paradox in that we possess today many effective drugs for the treatment of functional mental and emotional disorders, e.g., schizophrenia, depression and anxiety, but almost none for the treatment of the specific symptoms of organic brain syndrome, in spite of the fact that we do know a great deal about the morphological and physiological pathology of organic brain disease, but comparatively little about the physical substrate of the functional mental disorders.

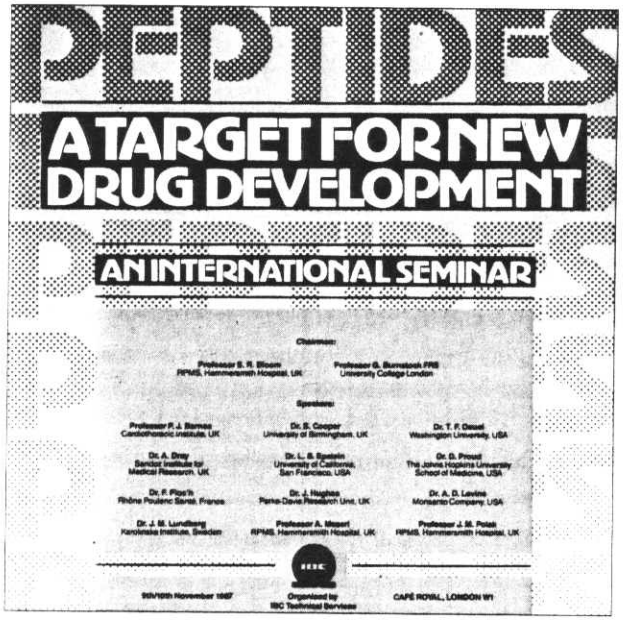

Fig. 4. - Announcement of an international seminar of peptide research. Note the equal participation of scientists from industry and academy.

In Western Nations, major programs to study and address problems associated with aging were established only in the mid '70s, when the special needs of the rapidly growing aged population were recognized. Research in aging has received support not only from governmental institutions but also from some of the largest and most creative pharmaceutical firms. Therefore, substantial progress has been made in exploring compounds for treating age-related disorders and in particular dementia.

In the laboratory, two main approaches are used to develop animal models for age-related disturbances: *a*) identify deficit in aged animals or tissue and attempt to correct with drugs; *b*) artificially induce neural/behavioral deficit in young animals and attempt to reverse or block with drugs [11].

Models in the first class utilize monkeys and rats, studying age-related changes such as retention of a previously learned task, number of neurons in a discrete brain region, *in vitro* release of dopamine, etc. Models in the second class are numerous and diversified and include ECT, anoxia, ischemia, aluminium toxicity, nutritional deficiences, pharmacological agents, brain lesions.

In several animal models evidence of beneficial activity has been obtained with three classes of drugs, namely, cholinomimetics, nootropics and certain neuropeptides. Even more interesting effects were obtained when a combination of these drugs was given to aged rats. In a task-sensitive to age-related loss of memory a combination of piracetam and choline induced striking improvement of the task (Fig. 5). Although the field of geriatric psychopharmacology is a controversial one, there is no

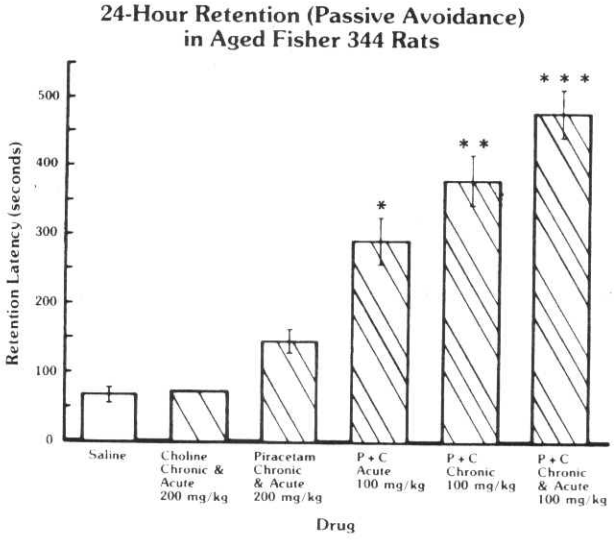

Fig. 5. - Effects of saline, choline (200 mg/kg), piracetam (200 mg/kg), or piracetam and choline (P+C; 100 mg/kg each) administered to aged rats (20 month old) prior to training and testing on a single-trial passive avoidance task. Acute refers to single injections 30 min prior to training and testing, whereas chronic refers to administration for 1 week (in their water) prior to training and testing ($^{*}p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.001$, according to Sheffé tests). (Reprinted by permission from Bartus *et al.* 1981, *Neurobiol. Aging* **2**: 105).

doubt that in the clinic these drugs have demonstrated their ability to improve mental performance in elderly humans. But I will not discuss the efficacy or claimed efficacy of the various drugs on the market. Instead, I would like to draw the attention to the fact that the efforts made by pharmacologists for a good evaluation of the effects of a drug in the laboratory are useless if they are not followed by a proper research in man. The problem, therefore, is to be solved by clinicians, to whom we must give all the possible help coming from basic research. From our investigations, for instance, it appears that the functional deficit in chronic cerebral syndromes has multi-faceted aspects. The therapeutic strategy will be therefore that of multiple pharmacological interventions to tackle the complex components of this disease.

It is likely that developments in the fairly near future will produce more effective nootropic drugs that may be used in combination with cholinergic precursors or other promising neurotransmitters and peptides. However, in order to establish the efficacy of such drugs unequivocally, we need a new methodology for testing nootropic agents in clinical trials.

The requirements before any drug might be tested are the following: *a*) they must have been shown to be free of any significant side effects of toxicity, as established in chronic animal studies and in Phase I clinical trials over a reasonable time period with aged subjects; *b*) they must prove, from experiments in animals, to be well promising for what concerns facilitation and protection of memory functions, increased learning and conditioning ability, and they must induce enhancement of normal cognitive and memory functioning in asymptomatic human volunteers.

Certain measures should, in my opinion, be routinely adopted as methodological principles for all future research on psychopharmacologic agents for the treatment of geriatric patients.

1) All clinical trials with nootropic drugs should be started with a 4-6 weeks open phase. After this period, only those patients who have shown some improvement should then be included in a double-blind controlled study, since this is the only specific way to determine whether a patient's intellectual impairment is still reversible. To include patients with irreversible conditions in a controlled trial would be irrational and misleading.

2) Only cognitive measures, *i.e.*, psychometric and neuropsychological tests, should be used to establish baseline and change scores.

3) The minimum period for clinical trials with nootropic drugs should be 12 weeks, since it has been repeatedly demonstrated that shorter periods are inadequate for clinical trials with chronic organic brain syndrome patients.

Through such efforts we may expect continued and accelerated progress in geriatric psychopharmacology, resulting ultimately in the development of safe and effective treatments for the major mental disorders of late life.

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