Egypt. J. Psychiat. (1981) 4 : 25–38

New Data on the Use of Antidepressant and Disinhibitory Drugs

By H. Loo, E. Zarifian, A. Tanios and P. Deniker

ABSTRACT

The authors studied the new findings concerning the utilization of the antidepressants and the disinhibitory drugs, by taking into consideration their mode of usage and their pharmacokinetics.

In the first part the authors demonstrated the utility of the pharmacokinetic studies and the plasmatic percentages of the antidepressants to allow for a better utilization and a more therapeutic efficiency.

Moreover they put emphasis on the indications of antidepressants according to such or such target symptom.

In the second part of the account the authors indicated the disinhibitory effect of antidepressants that can be at advantage in certain deficitary forms of schizophrenia.

Certain products (sulpiride) and certain original formulas (carpipramine) have specific disinhibitory actions.

INTRODUCTION :

The data exposed in this paper on the use of antidepressant and disinhibitory drugs will concern only the marketed molecules. However, the eventual progress opened by original substances must not be disregarded.

The Antidepressants :

The better knowledge of the therapeutic profile of each antidepressant drug, and of their biochemical mode of action presently allows a more rational use.

Furthermore, the possibility of the plasmatic dosage of tricyclic drugs and the pharmacokinetic data have modified several rules for prescription, that were empirical and unfit.

The precise characteristic of the antidepressant's therapeutic profile is the first and necessary element for the up-to-date prescription of antidepressants.

From the three clinical parameters for depression that have been isolated by Kielholz (1973), i. e. depressive mood, anxiety and psycho - motor inhibition, the antidepressants can be classified from a disinhibitory to a sedative pole.

In that way, Kielholz has characterized a certain number of antidepressants, according to their action on each of the main symptomatic groups of depression. As a whole, the percentage of efficiency of all the antidepressants is the same in the depressive syndromes (Kielholz, 1973). By gathering the controlled studies, Cole and Davis have objectified this similarity of the efficiency. The studies conducted with rating scales, or the comparative double blind studies, mainly consider the global scores at the end of the study. But a careful analysis all through the treatment shows that different clinical factors are at first modified according to the antidepressant used, even when at last all the pathological elements have disappeared. Prescribing a psychotonic antidepressant to an anxious - depressive patient risks to lead to an initial aggravation compelling to the stopping of the treatment; the result would then be classified as a failure, even though the antidepressant might have proven efficient. It is thus compulsory to link the clinical type of depression to the therapeutic spectrum of the antidepressant. This measure allows to wait for the delay of action of the drug, and not to the premature conclusion that there is a failure.

The delay of action is the second chief notion established by strict methodological studies. As a whole, the antidepressive action does not appear before 10 to 15 days, it is so for M.A.O. inhibitors as well as tricyclics. It now seems to be essential to wait for this delay before making a conclusion about the inefficacy of the medication (Loo and Zarifian, 1970; Deniker and Ginestet, 1973; Cole and Davis 1975).

Several years ago, it was advised to wait for 15 days to 3 weeks, " at efficient doses " by reference to standard dosages (Braithwaite et al., 1972); nowadays, it seems to be sensible to give a precision " at efficient plasmatic levels " (Braithwaite et al., 1973).

The shorter delays of action reported for some substances or for the use by the parenteral route appear to be established on partial improvements concerning anxiety or inhibition but not the mood.

The present data show that there is a lag of time between the pharmacological and the biochemical activity on one hand and the therapeutic response on the other hand. The inhibition of the monoamines re - uptake and their accumulation in the synaptic cleft quickly follows the absorption of a dose of antidepressant. There can be anticholinergic side-effects, contemporary to this biochemical activity; but the clinical response is delayed, which seems to show that there are other mechanisms that are put into action between the monoaminergic changes and the clinical variations. Enzymatic modifications and more recently variations of the sensitivity of the post - synaptic receptors have been evoked as possible links between the modifications of the monoamines and their action on the mood (Moussaoui, 1978; Zarifian, 1978).

The mode of action of the antidepressants must be taken into account for the up-to-date use of antidepressants.

Nowadays, different authors agree to think that the biochemistry of depression is beyond the frame of serotonin and norepinephrine. Nevertheless, the mode of action of the tricyclic antidepressants is mainly established on their capacity for the inhibition of the re - uptake of serotonin and/or norepinephrine. In 1970, Tissot (1970) drew a diagram on the mode of action of the tricyclic antidepressants. From experimental works, Waldmeyer **et al.,** (1976) have given a new classification of the antidepressants.

In front of a depression that resists a given product, it seems useful to turn to another product, the mode of action of which looks different from the one of the former substance. Indeed, the biochemical characteristic of the depression would be a better indication for choosing the substance to be used.

Beckman and Goodwin (1975) compare the results obtained in depressive patients who had been treated with imipramine and with amitriptyline, and draw a correlation between the biochemical data and the score of each type of antidepressant. The medium level of M.H.P.G is significantly lower in the patients responding to imipramine than in the patients who resist this product; the results are opposite with amitriptyline. The data about serotonin remain contradictory. In

depressed subjects, it nevertheless seems to be two modes of distribution of the level of 5 HIAA in the C.S.F. (Praag Von and Korf 1974). The patients with low levels of 5 HIAA in the C.S.F. would have the severest depressions. They would respond little to the antidepressants that have a preferential action on norepinephrine, such as nortriptyline (Asberg **et al.**, 1976; Praag Von and korf, 1974).

In the same way, the free portion of the plasmatic tryptophane has been studied to see whether serotonin was concerned in depressions (Coppen **et al.**, 1974; Cuche **et al., 1978**) and whether the precursors, tryptophane and 5 H.T.P. might have an antidepressant activity. There are no formal conclusions yet (Haefeley **et al.**, 1978).

In reality, **the biochemical characteristic** of depressions, especially by means of dosages in the C.S.F. proves to be difficult in daily practice. It must be limited to resistant cases (Renz **et al.**, 1971). For those reasons, some authors (for instance, Svensson and Waldeck, 1969; Praag Von and Korf, 1973; Deniker **et al.**, 1978) have tried to draw a clinical-biochemical correlation between the clinical symptoms and the monoaminergic systems which are eventually concerned. Schematically, the severe and suicidal depressions would be related to a deficit in serotonin, and the depressions with weariness effects and loss of the psychomotor initiative would rather depend on a norepinephrine deficit. This is a much discussed theory. It still has to be verified but it can sometimes help the prescription.

The M.A.O. inhibitors have a different action than tricyclics. They inhibit the destruction of monoamines, but their activity would be better noted on serotonin. The study conducted by Pare and cited by Moussaoui (1978) seems to point out that the cerebral level of serotonin increases with M.A.O. inhibitor but after 2 to 3 weeks. This acknowledgement explains once more the delayed onset of action. The M.A.O. inhibitor may prove its ability to act specifically in some depressions that resist the tricyclic substances. Hesitating about their use is thus not always legitimate.

At last, the mode of action of the antidepressants in the case of catecholamines may concern only serotonin and norepinephrine. Several points are in favor of a role played by dopamine in some depressions :

- ❋ the frequency of depressions in the course of Parkinson disease,
- ❋ the modifications of the level and of the circadian cycle of plasmatic tyrosine in depressed patients.
- ❋ the acknowledgement of the low level of H.V.A. in the C.S.F. of some depressed subjects, mainly when they are inhibited.
- ❋ the effectiveness of L. Dopa in some depressive symptoms (for instance, Tissot, 1970; Zarifian 1973; Waldmeyer **et al.**, 1976).

From these elements, the dopaminergic agonists such as bromocryptine appear as usable in mood disorders with a probable biphasic activity : by preferentially stimulating the pre-synaptic receptors, low doses of bromocryptine would oppose the synthesis and the synaptic availability of dopamine. At higher doses, it would then stimulate the post-synaptic receptors and would favor the dopaminergic transmission that increases the motor activity (Beckmann and Goodwin, 1975) in that, bromocryptine might present a sedative activity in mania, and an antidepressant activity in melancholia according to the posology used (Colonna **et al.**, 1978).

Some new antidepressants with a mode of action prevailing on dopamine appear to be interesting. There are for instance nomifensine and amineptine. Their therapeutic activity seems to associate antidepressive qualities and a stimulating potency that reminds of those which increase the locomotor activity noted in animals injected with dopaminergic agonists (for instance, Goodwin **et al.**, 1970; Deniker and Ginestet, 1973; Colonna, 1976; Barnes **et al.**, 1978).

The pharmacokinetic studies are essential for the modern use of antidepressants. They help in a better understanding of some causes of resistance or toxic manifestations with doses that appeared to be adequate.

Several pharmacokinetic elements of information are essential for a rational use of antidepressant substances :

the blood level of the substance (Potter and Goodwin, 1978); there is a tendency to define it as the blood range of efficiency that varies with the type of the substance shown in Singlas works

(1978). But the notion of efficient blood level remains an approximative indication. There are individual sensitivities that probably depend on many factors such as age and the genetic enzymatic activity. Moreover, the correlation between blood levels and therapeutic response has been criticized as useless, chiefly in the case of amitryptiline (Kenneth, 1978).

* the metabolism of the drug (its half-life, its volume of distribution and the way it is excreted) is useful in the establishment of the posology and the distribution of the takes. If renal deficiency seems to modify slightly the half life of the tricyclic antidepressants, hepatic deficiency increases it by slowing the catabolism (Sharples, 1975; Kenneth, 1978; Potter and Goodwin 1978).

When choosing a posology for a given subject, one must take into account the subject's hepatic functions. Moreover, only the free portion of the antidepressant substance is efficient, and the inactive portion bound to the proteins ranges from 75 to 95 according to the antidepressant studied (Sharples, 1975). But different factors, especially associated drugs can modify this binding (Sharples, 1975). The blood dosages have also allowed the determination of the necessary time for obtaining a steady state blood level under similar daily posology. This steady state must be taken into account to determine at what time the blood level must be estimated and to assess the delay of action.

* the ways for administering the antidepressant substance are very important too. The relation between the dose administered and the blood level is stricter with the parenteral route than with oral administration. The absorption is modified by many factors : The gastric emptying time, the gastric PH, the associated medications, and so on .. Those elements explain in part the important variations found in blood levels from one subject to another, with oral administration with the same posology, or in a single subject at different times (Coppen et al., 1974).

For a given posology, the blood levels found can range between 10 to 20 proportion according to the subjects (Cuche **et al.,** 1978). This acknowledgment explains sometimes toxic or unexpected levels found.

The strict clinical - pharmacological correlations can be discussed. But the contribution of pharmacokinetics doubtless helps a better understanding and a more efficient use of the antidepressant substances.

Antidepressant properties are considered as new substances.

The main ones are summed up. We shall only point out what we can expect from these substances.

Rubidum does not show the pharmacological profile of a true antidepressant, but it has an original spectrum of its own. Its mode of action may concern the biogenic amines, but this ion also acts on the mechanisms of the membrane transport, on the hydroelectrolytic balance, by its similarity to Potassium, and on some enzymatic systems such as ATPases (Boulenger **et al.,** 1977).

The eventual antidepressive action may be linked to those mechanisms that have already been evoked about Lithium.

- ❊ the eventually psychostimulant or antidepressive properties of B-stimulants and - alpha blocking substances essentially refer to an action on the post and or pre-synaptic receptors. The monoaminergic systems are concerned, but there may be specific modifications of the sensitivity or of the number of the receptor sites (Banerge **et al.,** 1977).
- ❊ Some authors consider the thyroid hormones as antidepressants. For some others, they are only able to potentialize the tricyclics. Presently, some authors evoke a possible action of thyroid hormones on the sensitivity of the noradrenergic receptors (Banerge **et al.,** 1978).
- ❊ The antidepressive properties of TSH, TRH and MIFI are questioned. Their close link with the monoaminergic systems led to evoke a mode of action using these systems. At the present time, a direct action of the hypothalamic peptide on the CNS is discussed (Goodwin et **al.,** 1970; Kastin **et al.,** 1974; Haefeley et **al.,** 1978). and especially " an

activity as neurotransmitters or modulators of synaptic transmission " (Ehrensing and Kastin, 1978).

The main point is not to make a list of all the virtually antidepressive substances. It must be noted that :

* Newer research suggests that we do not follow the pharmacological models that were similar to those drawn for imipramine,
* new biochemical mechanisms are thought to go beyond the frame of the quantitative variations of the biogenic amine.

These facts may help to find original substances which would be able to act on depressions that resist tricyclics and M.A.O. inhibitors.

Electroshock remains the most efficient antidepressant therapy : understanding of its mechanisms of action can also be a major indication.

The Disinhibitory Agents

The concept of a disinhibitory agent was created in France in 1956, by Broussolle who writes about the disinhibitory properties of prochlorpemazine (TEMENTIL). He describes disinhibition as the lifting of muteness, an improvement of activity and socialization, and a decrease of indifference in hebephreno - catatonic schizophrenics. Since then the term " disinhibitory " has been used for some neuroleptics presenting those properties, such as thioproperazine and pipotiazine. In their classification of neuroleptics, Deniker and Loo (1978) put them aside. Other authors think that the disinhibitory action is a part of the anti - psychotic activity.

The antidepressants are powerful " disinhibitors " in schizophrenias, but their stimulant property is often linked to an increase in anxiety or delirious activity. Modern studies have modified the concept of disinhibitory agents.

* The first factor in this modification is the attribution of the molecules with a stronger, more prevailing and more specific disinhibitory action. First appeared the sulpiride, then, more recently the carpipramine. Its chemical formula associates the nucleus of imipramine and the lateral chain of pipamperone, a butyro phenone. This last compound has a pharmacological profile where one can find some characteristics of the neuroleptics and of the antidepressants.

The clinical studies acknowledge its good disinhibitory activity in hebephrenia, but its antidepressive properties are still not proved (Deniker et al., 1978). The main point is to note that some products can more electively end a schizophrenic deficit without causing a sedation, nor any hyperkinetic or extrapyramidal phenomena.

* The second notion is the problem of the disinhibitory activity which is steady and intrinsically linked to the molecule, and this is for two reasons :

1) As time goes by, the disinhibitory activity always seems to fade away. This activity clearly appears but in the first weeks of the treatment. On the contrary, in lasting double blind studies, all the neuroleptics appear as efficient in schizophrenia. Potent hallucinolytic sedative substances such as haloperidol look identical to other products with a different profile.

2) The variations in doses seem to modify sometimes the profile of the neuroleptic substance. The increased posology of sulpiride and carpipramine, which are the most disinhibitory neuroleptics, lead to sedative and anti - delirious properties. On the other hand, the increased doses of haloperidol, can cause a disinhibition, even an agitated state with anxiety and delirious reappearance (Colonna, 1976).Thus, the new data show that the disinhibitory profile can be defined but for some doses. In fact, when it is possible, the use of dosage will help to refer the therapeutic profile to the blood levels. Then several neuroleptics might show a biphasic action with two poles : a hallucinolytic and sedative pole and a disinhibitory pole.

Thus, biochemical, metabolic and pharmacokinetic data help a better understanding of the action of antidepressant and disinhibitory agents. Modern use of these products asks for the knowledge of this fundamental informaion. To this effect, a progress in psychotropic chemotherapy cannot be thought of without a multidimensional approach together with basic researchers and clinicians.

REFERENCES

Asberg, M., Thorén, P., Treskman, L., Bertilsson, L. and Ringlarger, V. (1976) Serotonin depression : A biochemical sub-group within the affective disorders ? *Science*, **191**:478-480

Banerje, E.S.P., Kungl, S., Riggi, S. J. and Chanda, S. K. (1977) Development of bêta adrenergic receptor subsensitivity by antidepressants. *Nature*, **268** : 455-456

Banerge, S.P., Sharma V.K., Pointon, S.E. (1978) Regulation of adreno-receptors by thyroid hormone. *4 th International Catecholamine Symposium* Pacific Grove : California.

Barnes, T. R. E., Kidger, T. and Taylor P. J. (1978) On the use of dopamine agonists in tardive dyskinesia, *Amer. J. Psychiat.*, **135** : 132-133

Beckmann, H. and Goodwin, F. K. (1975) Antidepressant responses to tricyclics and urinary M.H.P.G. in unipolar patients : Clinical response to imipramine amitriptyline. *Arch. Gen. Psychiat.*, **32** : 17-21

Boulenger, J. P., Boutiller, H., Dachary, J. M., Gouzet M. A., Loo, H,, Raynaud, G., Scharbach, H. and Vadrot M. (1977) Point actuel sur le Rubidium. *Encephale* **3 , 4** : 333 – 356.

Braithwaite, R. A., Gouldingr, Theans, G. and Bailey J. (1972) Plasma Concentration of amitriptyline and clinical response. *Lancet*, **1** : 1297-1300.

Cole, J. O. and Davis, J. M. (1975) Antidepressant drugs. In Freedman, A.M., Kaplan, H. I. and Sadock B. J. (eds.), *" Comprehensive Textbook of Psychiatry "* Vol. 2. Baltimore : The Williams & Wilkins Company.

Colonna, L. (1976) Effets paradoxaux des Neuroleptiques *Encephale*, : **2 , 3** 197-200

Colonna, L., Petit M., Lepine, J. P., Boismare F. (1978) Etats depressifs, symptômes cliniques et hypothéses Monoaminergiques. *Encephale*, **4** : 5-7.

Colonna, L. Petit, M., Lepine, J. P. (1978) Interet de la bromocryptine dans les schizophrenies dysthymiques. *Encephale*, **4** : 115–117.

Coppen, A., Benjamin, W., Brooksbank, B. W., Eccleston E. G., Peet. M. and White S.G. (1974) Tryptophan metabolism in depressive illness. *Psychological Med.* **4** : 164–173.

Cuche, H., Rovei, V., Ben–Yacoub, A., Zarifian, E., Loo, H., Deniker, P., Morselli, P. L. (1978) Comparative Kinetic of chlorimipramine and amitriptyline administered by three different routes to depressed patients. Comm. présentée au 11 *th* C. I. N. P. Congress, Vienne 9–14 July (sous press),

Deniker, P. et Ginestet, D. (1973) Lacunes et besoins en matiers d'antidepresseurs tricycliques. *Therapie*, **28** : 235–248.

Deniker P., Loo, H., Zarifian E., Cuche H., Ben-Yacoub, A., Escandec., Bousqet, B. et Dreuxc. (1978). Mesure du tryptophan libre et lié aux proteines en pathologie mentale. *Ann. Medicopsychol.*, **136** : 169—175.

Deniker, P., et Loo, H. (1978) Les medicaments psychotropes : généralites et Classification. *Rev. Med.*, **19** : 199—213.

Deniker, P., Loo, H., Zarifian, E. Garreau, G., Bén-Yacoub, A. et Roux J. M. (1978) La Carpipramine, un medicament psychotrope particulier entre les neuroleptiques et les antidepresseurs (Etude ouverte sur 200 cas). *Ann. Medicopsychol.*, (Sous Presse).

Ehrensing, R. H. and Kastin, A. J. (1978) Dose related biphasic effect of propyl – lencyl – glycinamide in depression. *Amer. J. Psychiat.*, **5** : 562–566.

Goodwin, F. K., Murphy, D. L., Brodie, H. K. H. and Bunney Jr. W. E. (1970). L – Dopa, Catecholamines and behaviour : A clinical and biochemical study in depressed patients. *Biol. Psychiat.*, **2** : 341—366.

Haefeley, N., Schaffner, R., Burkard, W.P., Da Pradam., Keller, H. H,, Polc, P. and Richards J. G. (1978). Ro 11 – 2465, a potent and selective inhibitor of 5 — Hydroxy – Tryptamine Uptake. *Comm. presentée au 11 th C.I.N.P. Congress, Vienne* 9 – 14 July, 1978.

Kastin, A. J., Schally, A. V., Ehrensing, R. H. (1974) Endocrine and extra – endocrine studies of hypothalamic hormones. In Lederis, K., Cooper, K. E. (eds.), *Man in Recent Studies of Hypothalamic Function*. Basel: Karger S.

Kenneth, K. A, (1978) Tricyclic antidepressants. Mode of action and clinical use. In Lipton, M.A., Di Mascio A. and Killam K. F. (eds.), *Psychopharmacology. A Generation of Progress.* New York : Roven Press.

Kielholz, P. (1973). *La depression masquée.* (Hans Huber edit.) Berne, Stuttgart, Vienne.

Loo, H. et Zarifian, E. (1970) *Limites d'efficacité des chimiothérapies psychotropes.* Paris : Masson.

Moussaoui, D. (1978) Biochimie de la dépression *Encéphale*, **4**, **3** : 193 – 222.

Potter, W.Z. and Goodwin, F.K. (1978) Antidepressant drug levels and clinical responses. *Lancet*, **1** : 1049—1050.

Praag Von, H.M. and Korf, J. (1974) Serotonin metabolism in depression : Clinical application of the probenecid test. *Int. Pharmacopsychiat.*, **9** : 35 – 51.

Praag Von, H.M. and Korf, J. (1973) Cerebral monoamines

and depression : An investigation with the prebenecid technique. *Arch. Gen. Psychiat.*, **28** : 827 – 831.

Renz, A. Marano, C. and Matussek, N. (1971) Altered tyrosine day time plasma levels in endogenous depressive patients. *Arch. Gen. Psychiat.*, **25** : 359 – 363.

Sharples, D. (1975) Competition for plasma protein binding sites between phenothiazine tranquilizers and iminodibenzyl anti-depressants. *J. pharm. Pharmacol.*, **27** : 379—381.

Singlas, E. (1978) Principales données physicochimiques et pharmacocinetiques des médicaments usuels. *Rev. Med N' Special* 19—23.

Svensson, J.H. and Waldeck, B. (1969) On the significance of central noradrenaline for motor activity : Experiments with a new dopamine B-hydroxylase inhibitor. *Europ. J. Pharmacol.*, **7** : 278 – 282.

Tissot, R. (1970) Monoamines et régulations thymiques. *Confront. Psychiat.*, **6** : 87 – 152.

Waldmeyer, P.C., Greengrass, P. M., Baumann, P. and Maitrel. (1976) Effects of chlomipramine and other tricyclic antidepressants on biogenic amine uptake and turn – over. *Postgrad. Med J. Suppl.*, **3** : 33 — 39.

Zarifian, E. (1978) Hypothéses monoaminergiques dans la dépression. *Ann. Biol. Clin.*, (Sous Press).

Zarifian, E. (1973) Perspectives d'utilisation de la L-Dopa en Psychiatrie. Paris : These.

AUTHORS :

H. Loo, E. Zarifian, A. Tanios and P. Deniker. Service Hospitalo-Universitaire de Santé Mentale et de Thérapeutique (Pr. P. Deniker).

Hopital Sainte Anne — 1, rue Cabanis – 75014, Paris

الموجـــــز

معلومات جديدة عن كيفية استعمال العقاقير المضادة للاكتئاب والمضـــادة للتثبيط

لقد قام الباحثون بدراسة نتائج الأبحاث الجديدة المتعلقة بكيفيـــة استعمال العقاقير المضادة للاكتئاب والمضادة للتثبيط ، آخذين فى الاعتبار طريقة استعمالها وخصائصها من ناحية « الحركة العقاقيرية » والنســـبة البلازمية لاتاحة استخدام افضل وكفاءة علاجية أعلى لهذه الأدوية ، وفضلا عن ذلك فقد ركزوا على مؤشرات استخدام مضادات الاكتئاب على أساس النظر الى العرض المعنى كهدف العلاج .

أما فى الجزء الثانى من الدراسة ، فقد قام الباحثون باظهار المفعول المضاد للتثبيط لهذه العقاقير والذى قد يفيد فى حالة علاج حالات فصامية معينة ، واشاروا الى أن بعض المنتجـــات العقاقيرية لها مفعـــول نوعى مضـــــاد للتثبيط .

ABSTRAIT

Les Nouvelles Donneés de L'Emploi des Anti-Dépresseurs et des Médicaments Désinhibiteurs

Les auteurs étudient les nouvelles données concernant l'utilisation des anti-dépresseurs et des médicaments désinhibiteurs, en envisageant leur mode d'emploi et leur pharmacocinétique.

Dans la premiérepartie, les auteurs démontrent l'intérêt des études pharmacocinétiques, et des taux plasmatiques des anti-dépresseurs pour permettre une meilleure utilisation ; et une efficacité thérapeutique plus grande.

Ils mettent également en relief les indications des anti-dépresseurs selon leurs actions qui visent tel ou tel symptome-comme cible.

Dans la 2 éme partie de l'exposé, les auteurs indiquent l'effet desinhibiteur des anti-dépresseurs pouvant être mis à profit dans certaines formes déficitaires de la schizophrénie.

Certains produits (Sulpiride) et certaines formules originales (Carpipramine) ont une spécificité d'action désinhibitrice.