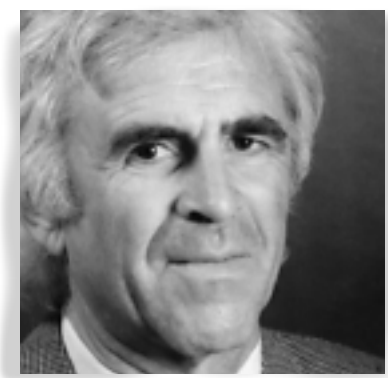
The therapeutic transnosological use of psychotropic drugs

Manfred Ackenheil, MD;
Lazara Karelia Montané Jaime, MD



Manfred ACKENHEIL

*The current clinical use of psychotropic drugs is transnosologically oriented. This is facilitated by the current classification of mental disorders (*International Classification of Diseases*, 10th Revision [ICD-10]) and is perhaps justified if depression and psychosis (taken here as examples) are considered as being complex syndromes with heterogeneous etiologies, but common pathogenesis, more than specific entities. However, this approach does not identify possible differences between specific psychiatric entities, which could in turn mask differences in therapeutic responses and, therefore, therapeutic outcome. This is compounded by the current disharmony between the nosological classification of diseases, drug development, clinical research, and therapeutic uses of psychotropic drugs. Functional pharmacology targeting abnormal behavioral traits could represent an avenue for future research and treatment.*

Keywords: *polypharmacy; depression; schizophrenia; antidepressant; antipsychotic; therapy*

Author affiliations: Nervenklinik der Universität München, Psychiatrische Klinik und Poliklinik, Munich, Germany (M. Ackenheil); Department of Pharmacology, Faculty of Medical Sciences, The University of the West Indies, St Augustine, Trinidad and Tobago (L.K. Montané Jaime)

Address for correspondence: Prof Manfred Ackenheil, Nervenklinik der Universität München, Psychiatrische Klinik und Poliklinik, Nußbaumstraße 7, 80336 Munich, Germany
(e-mail: ac@psy.med.uni-muenchen.de)

The nosological prescription of a drug refers to the effects of a substance on a specific pathological entity. The currently used diagnostic classification systems (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition [DSM-IV], as well as the *International Classification of Diseases,* 10th Revision [ICD-10]) are claimed to be "atheoretical," neglecting the etiology and pathophysiology of psychiatric disorders.[1] In actual "naturalistic" clinical practice, drugs are prescribed for a variety of psychopathological conditions that are not necessarily related to nosological categories.[2] The syndromal heterogeneity of the diagnostic constructs makes it impossible to demonstrate a potential syndromal specificity of a drug.

Historically, drugs have been developed empirically on the basis of clinical observations. The discovery of chlorpromazine for the treatment of schizophrenia in the early fifties by Delay and Deniker,[3] and of imipramine for depression a few years later by Kuhn[4] are such examples. On the other hand, new psychopathological syndromes have been identified by observant clinicians who recognized the unique actions of psychotropic drugs like clomipramine for the treatment of specific disorders such as obsessive-compulsive disorder (OCD)[5] or imipramine for panic disorders.[6,7]

Unlike other medical conditions, the etiology and pathophysiology of psychiatric disorders remain unknown. This is true despite the recent advances in the understanding of the function of the central nervous system (CNS) and in the field of biological psychiatry. Neurotransmitter imbalances in some areas of the CNS as well as neuroanatomical and neurophysiological abnormalities have been hypothesized to explain most of these psychiatric disorders, but this hypothesis has failed to be conclusively demonstrated. However, as no rational alternative explanation has been advanced for these disorders, the current pharmacological approach to the treatment of psychiatric disorders is based on trying to restore the observed dysfunction of central neurotransmitters.

Pharmacological aspects

Since the ICD-10 and DSM-IV classifications are based on clinical descriptions, they neglect biochemical and physiological abnormalities that are involved in the pathogenesis of disorders. The increasing knowledge of transmitter function in relation to behavioral pharmacology has suggested links to numerous psychiatric conditions. This "pathophysiological approach" to the development of new treatments is oriented more toward behavioral abnormalities than toward nosological syndromes. Pathophysiological approaches allow transnosological treatment because particular symptoms can occur in many different psychiatric disorders.

Behavioral abnormalities can be attributed to increased or decreased neuronal activity, and sometimes to alterations of specific transmitter receptors. This points to a role for functional pharmacology, which implies that, rather than nosological categories, one should treat basic disturbances in cognitive functions, impulse control, perception, information processing, and mood regulation.

Since in many cases monotherapy is insufficient to adequately treat the different nosological categories, naturalistic clinical practice requires that most patients be treated according to their symptoms with more than one drug.[2] The need for such multiple-drug therapy is due to many factors, such as multiple syndromes, comorbidity, and different target symptoms like negative and positive symptoms in schizophrenia. Frequently, comedication is prescribed without any pharmacological rationale.[8] Because of pharmacokinetic and pharmacodynamic interactions (potentiation or diminution), severe side effects may be induced or be the reason for absence of response. Better understanding of the principles of clinical pharmacology and education in clinical pharmacology are thus major tasks for the future.

The current prescription of psychotropic drugs appears to be well codified for most of the different ICD-10 categories *(Table I)*.

Selected abbreviations and acronyms

GABA	*γ-aminobutyric acid*
5-HT	*5-hydroxytryptamine = serotonin*
MAO	*monoamine oxidase*
MAOI	*monoamine oxidase inhibitor*
OCD	*obsessive-compulsive disorder*
SSRI	*selective serotonin reuptake inhibitor*
TCA	*tricyclic antidepressant*

Clinical treatment with antidepressants

Drugs for the treatment of affective disorders were discovered by serendipity. Imipramine was found to improve mood while being used in a protocol to search for an antipsychotic.[4] Iproniazid, a drug used in the treatment of tuberculosis, was likewise found to have beneficial effects on mood.[9] The former, a tricyclic antidepressant (TCA), and the latter, a monoamine oxidase inhibitor (MAOI), belong to two classes of drugs still in use today.

Depressive mood appears to be attributable to diminished activity of the dopaminergic, noradrenergic, and serotonergic neurotransmitter systems. Antidepressants restore the activity of these transmitters by inhibiting

	Treatment with		
ICD-10 categories	**AD**	**NL**	**BZD**
Organic, including symptomatic, mental disorders	+	+	+
Mental and behavioral disorders due to psychoactive substance use		+	+
Schizophrenia, schizotypic, and delusional disorders	+	+++	(+)
Affective disorders	+++	+	+
Neurotic, stress-related, and somatoform disorders		+	++
Behavioral syndromes associated with physiological disturbances and physical factors	+	+	
Abnormalities of adult personality and behavior	(+)	(+)	

Table I. The transnological prescription of antidepressants (AD), neuroleptics (NL), and benzodiazepines (BZD) according to ICD-10 categories (Section V).

reuptake in the presynaptic neurons. Additionally, the classic antidepressants have effects on other neurons (eg, histamine, acetylcholine), resulting in major side effects limiting their broader use. Depressive symptoms have been described in as many as 40 different disorders, which would imply that they could be used in all of them.[10]

Although the efficacy of TCAs has been well established, the high incidence of side effects and the high number of nonresponders or treatment-resistant patients represent drawbacks that have made it necessary to search for new drugs. The development of selective serotonin reuptake inhibitors (SSRIs) was the first attempt based on a pathophysiological approach. These drugs, which have similar efficacy, but less side effects than the TCAs, have become the preferred pharmacological treatment for depression. However, the high number of nonresponders and the delay in onset of response have limited their value. Some studies claim that they are less effective than TCAs in severe depression.[11] Therefore, antidepressants with dual action have been developed. Today, up to seven different classes of antidepressants are available, which mainly differ in their selectivity for the respective monoamines and their receptors.[12]

These discoveries have intensively stimulated biochemical-pharmacological research into the mechanism of action of antidepressants. Findings from these investigations suggest that enhanced activity of the central noradrenergic and/or serotonergic transmitter system is essential for the clinical antidepressant action. Such enhancement could be achieved either presynaptically by blocking α_2-adrenergic receptors, or in the synaptic cleft by inhibiting the transmitter reuptake or the main metabolic enzyme monoamine oxidase (MAO). The increased transmitter concentration in the synaptic cleft after chronic treatment leads to a downregulation of postsynaptic β-receptors, sometimes modulated by interaction with neuropeptides and hormones.[13,14]

In addition, depending on the antidepressant used, the sensitivity of 5-HT_{2A}, somatodendritic 5-HT_{1A}, or noradrenergic α_1 receptors may be reduced, leading to an overall increase in serotonin transmission. Such receptor alterations appear to provide the best explanation for the delay in clinical antidepressant response. The introduction of new classes of antidepressants has led to renewed thinking about their mechanism of action. Recent investigations of second messenger systems such as the adenylate cyclase system and the phosphatidylinositol system are very promising. Antidepressant drugs, including the mood stabilizers lithium and carbamazepine, modulate both of these second messenger systems, which in turn modulate the phosphorylation status of neuronal proteins via protein kinase. The outcome is a positive alteration of the gene expression of the relevant biochemical structures (enzymes, transporters, receptors), thus restoring the normal function of the respective neuronal systems.

Thanks to clearer understanding of the function of this complex serotonergic system we now know that a great number of normal and abnormal behaviors can be attributed to dysfunction of the serotonergic neurons, in addition to their role in depression. The limited number of serotonin neurons in the brain (approximately 300 000) suggests that their role is mainly a modulating one. This implies that they act to either dampen or accelerate a given type of behavior. Drugs targeting the serotonergic system are therefore able to influence many kinds of behavior abnormalities *(Figure 1)*.

Concerning the norepinephrine system, there have been attempts to link noradrenergic dysfunction to subgroups of depression. As already mentioned, some forms of depression are assumed to be accompanied by reduced noradrenergic activity. However, this is a matter for discussion, and some forms of depression may even be accompanied by increased noradrenergic function. It is hypothesized that noradrenergic neurons in the locus ceruleus are activated or increased in anxiety and panic disorders. Conversely, a norepinephrine deficit is invoked to explain disturbances of attention, psychomotor retardation, and impaired vigilance.

Some antidepressants also increase dopaminergic neuron activity, either directly or indirectly, by acting on serotonergic and noradrenergic pathways. Dopamine, a major transmitter of the reward system also plays a role in depressive states. Dopaminergic antidepressants could be of interest in some subgroups of depression, but so far no such drugs are available in Europe. However, in some patients with refractory depression, dopaminergic drugs like amphetamine have some beneficial effects.[15]

It is difficult to link the three monoaminergic systems to specific psychiatric disorders. The three systems do not function independently of each other. Neuronal circuits establish functional relationships between serotonergic, noradrenergic, and dopaminergic systems, which explains why deficiency in one system impairs the other

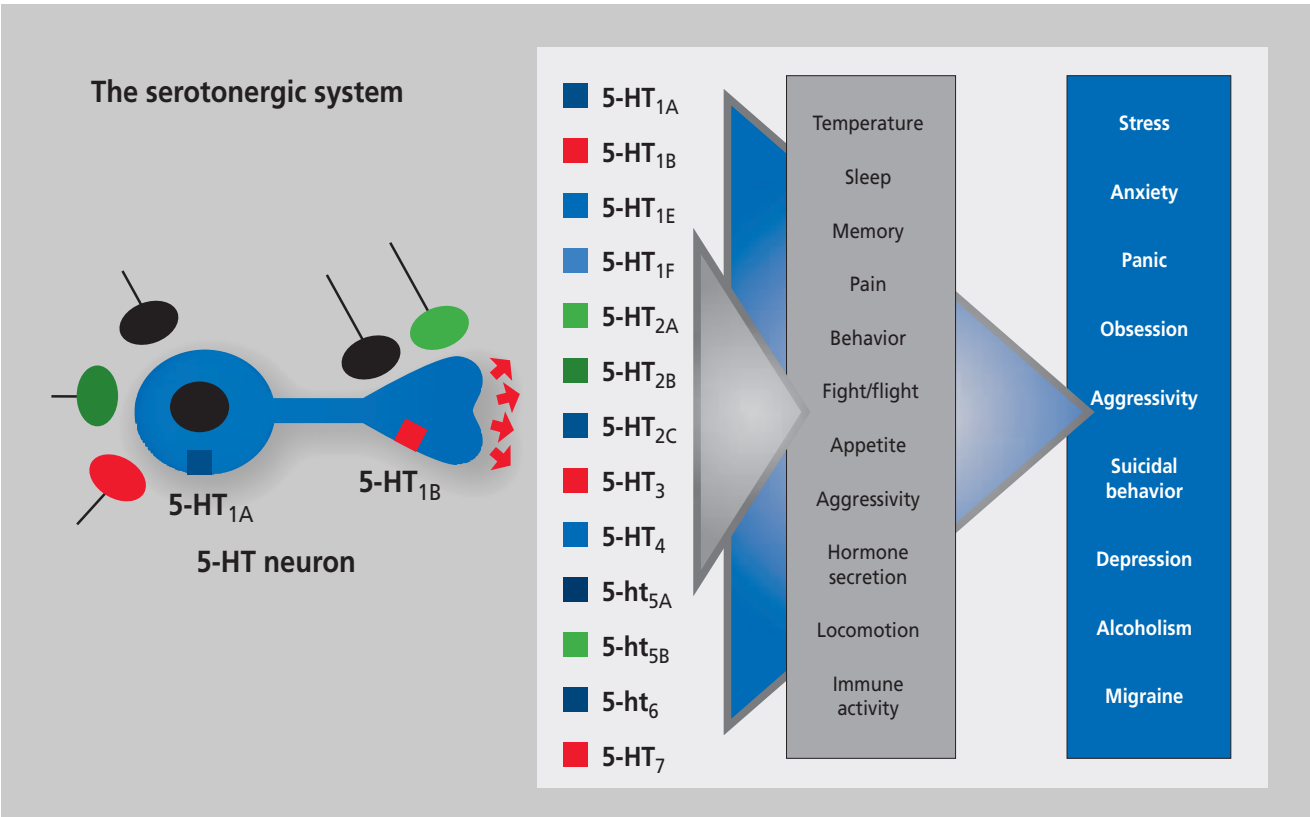


Figure 1. Serotonergic receptors, behaviors, and psychiatric disturbances. After G. Fillion, with permission (ubpublished data).

systems as well, and why even specific drugs like the SSRIs are also able to modulate the other systems.

The variety of the clinical uses for the newer antidepressants may necessitate a reexamination of traditional diagnostic categories and of theories on the way antidepressants work.

Antidepressant drugs are used in a wide range of psychiatric disorders. Empirical evidence in the 70s suggested that the nonselective serotonin antidepressant clomipramine improved symptoms of OCD.[5] Newer generations of antidepressants with fewer side effects have proved to be even more active in OCD.[16,17] Furthermore, 5-HT_{1A} serotonin agonists are being investigated in general anxiety disorders.[18] 5-HT_2 receptor antagonists are being tested on schizophrenic symptoms, anxiety, or dysthymia.[19] Other potential indications for SSRIs and the new generation of antidepressants are panic disorders, premenstrual dysphoric disorder, eating disorders, substance abuse disorder, chronic pain, dementia, and personality disorders with aggression or impulse disturbances, and general anxiety disorders.[20]

Depressive symptoms are frequently diagnosed in patients with schizophrenia and have been described in schizoaffective disorders. They can also occur after the acute phase of schizophrenia or after neuroleptic treatment. SSRIs seem to be useful in combination with antipsychotics to treat this condition.[20] This may be the reason why such patients are frequently (50% of cases) treated simultaneously with antipsychotics and antidepressants.[2]

Antidepressants are also useful in the treatment of a group of disorders that may be phenomenologically and genetically related to major depression, such as fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder.[21] It is likely that the etiology of depression (as a symptom) in these disorders is similar to that of major depression as an entity, and therefore would explain the efficacy of SSRIs. Although not impossible, it would be contrary to expectation if the

mechanism of antidepressant effect was independent of the mechanism of depression in migraine, premenstrual dysphoric disorder, and other conditions. And it would be even more difficult to believe that different, chemically unrelated antidepressant drugs, share the same pharmacological properties while having different mechanisms of action.[12]

Treatment of schizophrenia and other psychiatric disorders with antipsychotics

Genetic and biological studies show that schizophrenia is a heterogeneous disease. Disturbances in neurodevelopment and/or abnormal immune function may be responsible for schizophrenic symptoms.[22] Additionally, abnormal dopamine, norepinephrine, and serotonin transmitter activities in some areas of the brain may be pathophysiologically relevant to some schizophrenic syndromes. Other theories put forward disturbances in the glutamatergic and GABAergic circuits. Because of this heterogeneity and the impossibility of characterizing clinical subgroups of schizophrenic patients, none of these theories has been conclusively proved so far.[23,24]

The discovery of chlorpromazine[3] for the treatment of schizophrenia opened new perspectives for the care of psychiatric patients. Unfortunately, chlorpromazine and the other classic neuroleptics produce side effects that limit their widespread use. For many years, the dopamine hypothesis, based on the assumed mechanism of action of these compounds, was the predominant theory.[23]

The introduction of new atypical neuroleptics such as clozapine, which was the first one, paved the way for revisiting the dopamine hypothesis of schizophrenia and related theories on the mechanism of action of neuroleptics. To explain the unique features of clozapine, new theories have been put forward, partly in relation to interference with dopamine receptor subtypes and partly in relation to interference with other neurotransmitters such as norepinephrine and serotonin.[25] The nonspecificity of second-generation atypical neuroleptics for the dopaminergic system, the therapeutic ineffectiveness of some selective dopaminergic drugs, the lack of success of genetic studies targeted to the dopaminergic system, and the disappointing biochemical findings in schizophrenic patients have resulted in alternative theories of pathogenic causes of schizophrenia being proposed, opening up new perspectives for the development of future drugs. Based on neuropathological and neuroanatomical findings and in concordance with the revised dopamine hypothesis, new models have been postulated focusing attention on the excitatory amino acid γ-aminobutyric acid (GABA) and the most ubiquitous amino acid transmitter in the brain, glutamate.[26]

Psychotic symptoms of schizophrenia have been divided into negative symptoms (blunted affect, anhedonia, asociality, inability to initiate and carry out complex tasks to completion), which seem to be related to cortical hypofunction, and which, in turn, may be associated with decreased mesocortical dopaminergic activity and positive symptoms (hallucinations, delusions, and thought disorders). They also appear in disorders other than schizophrenia as well as many nonpsychotic disorders, and are related to increased activity of the subcortical striatal dopaminergic neurons.

Antipsychotic drugs are used in many psychiatric disorders other than schizophrenia. Before lithium was considered as the standard treatment for bipolar depressive and manic patients,[27] the pharmacological strategies for bipolar disorder included neuroleptics and antidepressants. They are now mainly used to treat the psychotic symptoms present during one of the poles of the disorder, or as an adjunctive treatment when other alternatives have failed. There have been several reports that clozapine may be more effective in patients with mania and schizoaffective disorder than in patients with schizophrenia. Refractory rapid-cycling and dysphoric mania also seem to improve with clozapine. Both psychotic and mood symptoms respond well to clozapine monotherapy.[28] Preliminary reports suggest that the newer atypical antipsychotics olanzapine[29] and sertindole may also be effective in stabilizing mood or in the management of affective symptoms.

Refractory psychotic depression has also been successfully treated with clozapine monotherapy.[28]

The occurrence of psychotic symptoms is frequent during the evolution of idiopathic Parkinson's disease and other parkinsonian syndromes. They seem to be related to interactions between the underlying neuropathological manifestations of the syndromes and the adverse effects associated with chronic antiparkinsonian drug administration. In patients with advanced Parkinson's disease, there is also a high prevalence of affective comorbidity. Classic neuroleptics may improve the symptoms, but usually worsen the parkinsonism. Clozapine has been used successfully since 1985 with only few extrapyramidal

effects.[30] Olanzapine has been reported to be effective in the suppression of psychotic symptoms in these patients, but the currently available dose increments may result in an exacerbation of motor disability.[31]

Transnosological use of psychotropics: drug development and clinical research

As mentioned above, since no solid alternatives have emerged from biological research to replace the current hypothesis regarding the pathogenesis of psychiatric disorders, the development of new psychotropic drugs remains based on the restoration of the imbalance in the monoaminergic system.

This is exemplified by the development of the new antidepressants. The postulate that depression results from a dysfunction in the noradrenergic, serotonergic, and dopaminergic systems leads logically to the attempt to design antidepressants that act mainly on one of the neurotransmitter systems. The idea is to increase selectivity without compromising efficacy, while at the same time reducing the side effects that result of interactions with these and other neurotransmitter systems. Thus, blockade of serotonin reuptake gave rise to the now well-known SSRIs. A new class of drugs, which selectively inhibit the reuptake of norepinephrine, was recently introduced onto the market. However, experience with psychotropic drugs acting on either the noradrenergic or the serotonergic systems suggest how important it is (at least in certain situations) to act on both systems at once. Research was therefore undertaken to develop new antidepressants with a dual action on these systems. This functional pharmacological approach focuses on symptoms rather than nosology.[32,33]

Conclusion

Although drug development tries to focus on specific mechanisms involved in depression and its symptoms, clinical research is not nosologically but transnosologically oriented. The tools used to monitor therapeutic response in clinical trials are usually rating scales that evaluate the depressive or psychotic state rather than treatment efficacy on a specific entity. Efficacy, nosology, and duration of treatment are based on the antidepressant effect, and, therefore, in many of the specific entities where they are presently used, these variables have not been confirmed. Similarly, in most trials focusing on therapeutic outcome, there are no differences between different drugs belonging to the same therapeutic group. The current situation is therefore characterized by disharmony prevailing between psychotropic drug development, nosological classification of diseases, clinical research, and therapeutic uses of psychotropic drugs. ❑

REFERENCES

1. van Praag HM. The impact of classification on psychopharmacology and biological psychiatry. *Dialogues Clin Neurosci.* 1999;1:141-151.
2. Rittmansberger H, Meise U, Schauflinger K, Horvath E, Donat H, Hinterhuber H. Polypharmacy in psychiatric treatment. Patterns of psychotropic drug use in Austrian psychiatric clinics. *Eur Pyschiatry.* 1999;14:33-40.
3. Deniker P. Discovery of the clinical use of neuroleptics. In: Parnham MJ, Bruinvels J, eds. *Discoveries in Pharmacology.* Vol I. *Psycho- and Neuropharmacology.* Amsterdam, The Netherlands: Elsevier; 1983:163-180.
4. Kuhn R. Über die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G22 455) [Treatment of depressive states with an iminodibenzyl derivative (G22 455)]. *Schweiz Med Wochenschr.* 1957;35/36:1135-1140.
5. Clomipramine Collaborative Study Group. Clomipramine in the treatment of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry.* 1991;48:730-738.
6. Bougerol T, Farisse J. Pharmacotherapy of panic disorder. *Encephale.* 1996;22(5, special issue):46-53.
7. Sheehan DV. Current concepts in the treatment of panic disorder. *J Clin Psychiatry.* 1999;60(suppl 18):16-21.
8. Nichol MB, Stimmel GL, Lange SC. Factors predicting the use of multiple psychotropic medications. *J Clin Psychiatry.* 1995;56:60-66.
9. Crane GE. Iproniazid (Marsilid) phosphate: a therapeutic agent for mental disorders and debilitating diseases. *Psychiatr Res Rep Am Psychiat Assoc.* 1957;8:142-152.
10. De Smet Y. Indications for new antidepressants with reference to ICD-10: a waggish question or the future of psychiatry? *Encephale.* 1997;23:77-82.
11. Stahl SM. Are two antidepressant mechanisms better than one? *J Clin Psychiatry.* 1997;58:339-440.
12. Stahl SM. Basic psychopharmacology of antidepressants. Part 1. Antidepressants have seven distinct mechanisms of action. *J Clin Psychiatry.* 1998;59(suppl 4):5-14.
13. Ackenheil M. The mechanism of action of antidepressants revised. *J Neural Transm.* 1990;32(suppl):29-40.
14. Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. *J Clin Psychiatry.* 118;59(suppl 14):11-14.
15. Stotz G, Woggon B, Angst J. Psychostimulants in the treatment of therapy-resistant depression: review of the literature and findings from a retrospective study in 65 depressed patients. *Dialogues Clin Neurosci.* 1999;1:165-174.
16. McDougle CJ, Goodman WK, Price LH. The pharmacotherapy of obsessive-compulsive disorder. *Pharmacopsychiatry.* 1993;26(suppl 1):24-29.
17. Dolberg OT, Iancu I, Sasson Y, Zohar J. The pathogenesis and treatment of obsessive-compulsive disorder. *Clin Neuropharmacol.* 1996;19:129-147.

Prescripción de carácter transnosológico de los psicofármacos

El uso actual de los psicofármacos tiene una orientación transnosológica. Esto está favorecido por la actual clasificación de los trastornos mentales (Clasificación Internacional de Enfermedades, *décima versión [CIE 10]) y se justifica si la depresión y las psicosis (tomadas aquí como ejemplos) son consideradas complejos sindromáticos con una etiología heterogénea, pero con una patogénesis común, más que entidades clínicas específicas. Sin embargo, este enfoque no identifica las posibles diferencias entre cuadros psiquiátricos específicos, lo que puede llevar a enmascarar las diferencias en las respuestas terapéuticas y por lo tanto, en la evolución del tratamiento. Esto se complica con la actual disarmonía entre la clasificación nosológica de las enfermedades, el desarrollo de medicamentos, la investigación clínica y el empleo terapéutico de psicofármacos. Una farmacología funcional orientada a los rasgos de conducta anormal podría representar un camino para la investigación y terapéutica futuras.*

L'utilisation thérapeutique transnosologique des psychotropes

L'utilisation actuelle des psychotropes en pratique clinique est essentiellement transnosologique. Cette attitude est favorisée par la classification en vigueur des maladies mentales (Classification Internationale des Maladies, 10e édition [ICD-10]), et se justifie sans doute si l'on considère que la dépression et la psychose (évoquées dans le présent article) représentent plus des syndromes complexes, dont les étiologies sont hétérogènes mais la pathogenèse commune, que des entités spécifiques. Néanmoins, cette approche ne permet pas de différencier les entités psychiatriques spécifiques, ce qui peut conduire à masquer les différences dans les réponses thérapeutiques et, par conséquent, dans les résultats obtenus. Ceci est aggravé par le manque d'harmonisation actuel qui existe entre la classification nosologique des maladies, le développement des médicaments, la recherche clinique et les utilisations thérapeutiques des psychotropes. L'approche ciblée des traits de comportements anormaux par la pharmacologie fonctionnelle pourrait représenter une voie d'avenir pour la recherche et la thérapeutique.

18. Van Vliet IM, Westenberg HG, den Boer JA. Effects of the 5-HT_{1A} receptor agonist flesinoxan in panic disorder. *Psychopharmacology (Berl).* 1996;127:174-180.
19. Reyntjens A, Gelders YG, Hoppenbrouwers ML, Vanden Bussche G. Thymosthenic effects of ritanserin (R55 667), a centrally acting serotonin S2 receptor blocker. *Drug Dev Res.* 1986;8:205-211.
20. Finley PR. Selective serotonin reuptake inhibitors: pharmacologic profiles and potential therapeutic distinctions. *Ann Pharmacother.* 1994;28:1359-1369.
21. Gruber AJ, Hudson JI, Pope HG Jr. The management of treatment-resistant depression in disorders on the interface of psychiatry and medicine. Fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder. *Psychiatr Clin North Am.* 1996;19:351-369.
22. Müller N, Riedel M, Ackenheil M, Schwarz M. The role of immune function in schizophrenia: an overview. *Eur Arch Psychiatry Clin Neurosci.* 1999;249(suppl 4):62-68.
23. Carlsson A. The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology.* 1998;1:179-186.
24. Reynolds GP. Developments in the drug treatment of schizophrenia. *Trends Pharmacol Sci.* 1992;13:117-121.
25. Ackenheil M. Clozapine—pharmacokinetic investigations and biochemical effects in man. *Psychopharmacology.* 1989;99:32-37.
26. Ackenheil M. Beyond dopamine, what could be the place of other neurotransmitters in the development of antipsychotic agents? *Medicographia*. 1998:20:101-106.
27. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness. *Arch Gen Psychiatry.* 1982;39:1065-1069.
28. Ranjan R, Meltzer HY. Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. *Biol Psychiatry.* 1996;40:253-258.
29. Tohen M, Gannon KS, Sanger TM, et al. Safety of the novel antipsychotic olanzapine in the acute treatment of Bipolar I Disorder. *Scientific Abstracts of the American College of Neuropsychopharmacology 37th Annual Meeting;* December 14-16, 1998; Puerto Rico. In press.
30. Auzou P, Ozsancak C, Hannequin D, Moore N, Augustin P. Clozapine for the treatment of psychosis in Parkinson's disease: a review. *Acta Neurol Scand.* 1996;94:329-336.
31. Juncos JL. Management of psychotic aspects of Parkinson's disease. *J Clin Psychiatry.* 1999;60(suppl 8):42-53.
32. Pfohl B. Disease, disorder, syndrome or symptom: which shall we treat? *Harv Rev Psychiatry.* 1996;3:356-358.
33. Jouvent R. De l'approche dimensionnelle à l'étude transnosographique des psychotropes [Dimensional approach to the transnosographic study of psychotropic agents]. *Encephale.* 1995:21(special issue 1):39-43.