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Nosology and Nosography

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Dialogues in clinical neuroscience

Editorial

Dear Colleagues,

For the best part of the last two centuries renowned psychiatrists have invested considerable energy in the attempt to develop a perfect classification of mental disorders. This has proved almost as elusive as the quest for the Holy Grail in medieval literature. One reason for this lack of success is probably the fact that the cause of most mental disorders is unknown; consequently, it was, and probably still is, impossible to construct a classification on an etiological basis. The validity of such classifications is often short-lived as they are soon superseded by the emergence of new theories. The classifications of the previous decades have withstood the test of time very poorly. For instance, those of the sixties and seventies now seem too heavily influenced by the prevailing ideologies of the time. One may venture that the psychiatric nomenclatures that were taught in medical schools until 1980—the year when the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III) was published by the American Psychiatric Association—offered no clear improvement over what the German psychiatrist Emil Kraepelin had already proposed in the 7th and 8th editions of his *Textbook of Psychiatry* in 1903 and 1915.

Because of this impossibility of achieving a valid etiological classification of mental disorders, our current diagnostic systems, such as the *International Classification of Diseases, 10th Revision* (ICD-10) of the World Health Organization, or the 4th edition of the DSM, have deliberately adopted a descriptive and "atheoretical" standpoint—that is, they are neutral with respect to etiological theories. Such an approach lessens the risk of generating nomenclatures based on assumptions that will be disproved by future research. However, we often tend to lose track of a premise paramount in the mind of the creators of the DSM or ICD, namely, that although diagnostic nomenclatures are supposed to facilitate communication, they are not synonymous with real diseases. The categories listed in DSM-IV or ICD-10 are often heterogeneous, and the diseases underlying them are often unknown. A simple term like schizophrenia or major depression may designate distinct illnesses differing in etiology, course, and response to treatment.

Oblivious to the fact that psychiatric nomenclatures were devised primarily for communication and statistics—rather than research and science—pharmaceutical companies, drug regulatory agencies, and national health authorities tend to extend their field of application to situations where they no longer are valid. This confusion between diagnostic categories and real diseases has stultifying effects on drug development, health care funding, and approval of new drugs. Thus, a diagnostic label is now often misused to determine which type of drugs the physician may give his patients and how long he is allowed to keep them in hospital. A diagnostic code cannot predict the response to pharmacological treatment and has only limited usefulness for clinical drug trials. Insistence on using traditional diagnostic categories may hamper the discovery of innovative drugs.

Possible ways of improving diagnosis for research and treatment purposes might include: (i) weighting symptoms according to their duration, severity, and mode of onset, and better defining their hierarchical relationships; (ii) placing more emphasis on detailed patient life histories (psychobiographies) and personality assessments, which the mere juxtaposition of Axis I and II diagnoses currently fails to adequately take into account; and (iii) characterizing patients in drug trials by complementing the imprecise diagnostic categories now in use with additional information from psychometric testing, pharmacogenetics, neurobiology, electrophysiology, brain imaging, etc.

Since diagnostic classification occupies such a fundamental place in our clinical practice and the treatment of our patients, we have elected to devote this issue of *Dialogues in Clinical Neuroscience* to the "transnosological" approach.

Sincerely yours,

Jean-Paul MACHER, MD

Marc-Antoine CROCQ, MD

Dialogues in Clinical Neuroscience is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material.

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Conceptualization of the liability for schizophrenia: clinical implications

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Definitive knowledge about the pathogenesis of schizophrenia remains elusive in spite of dramatic advances in molecular biology techniques. Molecular genetic studies, in particular, have yielded many promising results. However, there is an increasing discrepancy between current classification systems (DSM-III/IV and ICD-10), on which these studies were based, and recent discoveries in the genetics of schizophrenia, which begs for a broader conceptual outlook. The concept of "schizotaxia" advocated by Ming Tsuang exemplifies this new approach.

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Treatment-resistant depression is a major challenge in psychiatry. The antidepressants usually prescribed are often not effective at all, making it necessary to experiment with new treatment approaches like combination therapy. An unusual solution relating to psychostimulants is presented here. Evidence that the dopaminergic system plays a role in depression may enhance the value of such a strategy in the future, particularly in view of the lack of dopaminergic antidepressants.

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Current pharmacological treatment, especially in drug trials, is nosology-oriented, as a consequence of the requirements stemming from regulatory authorities. This, however, is at variance with the "endogenous" nature of psychiatric disorders, which, similar to somatic medicine, are likely to result from different causes, thus requiring different types of therapy. This explains why patients are frequently treated in a different way in clinical practice than in trials. Conversely, differing nosological categories may be treated with the same class of psychotropic drugs. All this has theoretical and practical implications regarding our concepts in psychiatry, chief among which is the future need to treat psychiatric patients according to the same principles as in other disciplines of medicine.

Validity of nosological classification

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This paper uses the example of schizophrenia to look at the pros and cons of expert clinician diagnosis, based on a holistic approach, in comparison with algorithmic diagnosis, based on the DSM-IV and ICD-10 classification systems. The author highlights the poor correlation between the two types of diagnostic processes, and points out the low validity and limitations of the DSM-IV and ICD-10 classifications.

Diagnostic classification of psychiatric disorders and familial-genetic research

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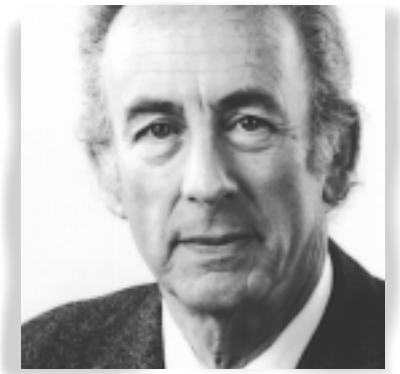
In principle, specific phenotypes should aggregate in families with high vulnerability to a particular disorder. However, the relevance of the boundaries between the different psychiatric disorders, according to the ICD-10 or DSM-IV, as well as that of comorbidity, is still unclear. The author looks at these issues from the point of view of genetic epidemiological studies of schizophrenia, and highlights the discrepancy between the range of phenotypes transmitted in families of schizophrenics and the current diagnostic boundaries. Progress in familial-genetic research should help to better identify the various subtypes of psychiatric disorders as well as the boundaries (when relevant) between the different clinical entities.

Manfred Ackenheil, MD

The impact of classification on psychopharmacology and biological psychiatry

Herman M. van Praag, MD, PhD



Nosological classification in psychiatry, as it is currently applied, does not facilitate biological and psychopharmacological research.

- *Syndromal acuity has disappeared. Consequently, it is impossible to determine: (i) whether a particular drug affects a particular symptom configuration; (ii) what exactly the behavioral correlate of a particular biological disturbance is. The problem of unfocused diagnoses is greatly magnified by the phenomenon called comorbidity.*
- *The boundary between distress and disorder is ill-defined.*
- *Symptom configuration and certain nonsymptomatological variables such as duration and severity are prematurely linked, so as to conceptualize categorical entities. The validity of those constructs has not been sufficiently demonstrated. This undermines the validity of biological studies and leads to "nosologomania," ie, an ever-growing series of undervalidated psychiatric "disorders."*
- *Symptoms are grouped horizontally as if they all had the same diagnostic "valence." This, however, is highly unlikely.*
- *The nosological disease model is unconditionally and uncritically accepted. Alternative models are ignored, particularly the reaction-form model, though it has substantial heuristic value, and deserves to be thoroughly scrutinized.*

(Research) strategies to remedy this situation are pointed out.

Premises of the nosological disease model

The nosological disease model has dominated psychiatry ever since its introduction in 1863 by Kahlbaum.[1] However, this model is not an empirical one, based as it is on the core premise that disturbances of the "psychic apparatus" manifest themselves as discrete entities. In actual fact, this core premise itself rests on two "subpremises."

The *first* "subpremise" is that psychiatric disorders are characterized by a particular symptomatology, course, outcome, treatment response, and, in principle, pathophysiology. The words "in principle" are important to stress that little is known, so far, about the neurobiological basis of mental disorders. The word "particular" implies that mental disorders are intrinsically stable, so that recognizing a particular type of syndrome allows reliable predictions to be made concerning course, outcome, treatment response, and (in principle) pathophysiology, and, conversely, that if the pathophysiology is known, then predictions can be made relative to possible type(s) of resulting syndrome(s), course, outcome, and treatment response.

The *second* "subpremise" postulates that each disease entity can be distinguished and individualized with respect to neighboring diagnostic constructs.

It is therefore based on this core premise and its two attendant "subpremises" that mental diseases have been conceived of as discrete entities, and that, accordingly, diverse taxonomic classifications of mental disorders have been put forward.

Keywords: *diagnosis; classification; nosology; reaction-form disease model; comorbidity; primary psychiatric symptom; secondary psychiatric symptom; psychogenesis; "nosologomania"*

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Antinosology and neonosology

The nosological disease model encountered its first serious opponent with the advent of psychoanalytical philosophy during the first half of the 20th century. This school of thought regarded (deviant) psychological development and related inner conflicts as the decisive generators of abnormal behavior, and set itself the task of analyzing and diagnosing them. Phenomenology was deemed of subordinate importance, and pathophysiology inconsequential. By definition, an individual's life course and inner conflicts are essentially unique, making generalizations about mental disorders well-nigh impossible, and a taxonomy of mental disorders virtually meaningless. Of particular note is the fact that psychoanalytic schools remained mostly outside mainstream academic psychiatric centers in Europe, whereas in the USA they were to dominate academic psychiatry for many years.

During the 70s, a nosological revival set in, heralded by the publication of Feighner's *Research Diagnostic Criteria* (1972),[2] which reached its pinnacle in 1980 with the publication of the 3rd edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III). The taxonomy of DSM-III was constructed on nosological principles and defined a large number of discrete disorders based on symptomatological and some non-symptomatological criteria, such as duration, severity, and course. The DSM system was based on consensus opinion and reviews of the literature rather than on systematic empirical studies. This was inevitable inasmuch as doing otherwise would have set back for years the publication of the first operationalized and standardized psychiatric taxonomy. Since DSM-III there have been two revisions (DSM-III-R and DSM-IV), yet without confirmation of the numerous diagnostic constructs that had been introduced. Validating studies were unable to keep pace with the rate of publication of new versions, and the field studies carried out toward this end were simply insufficient.

The *International Classification of Diseases* (ICD), drawn up by the World Health Organization (WHO), followed a similar fate. The 10th edition of the ICD (ICD-10), completed in the 80s, operationalized the diagnostic criteria for mental diseases and formulated decision trees to arrive at particular diagnoses. ICD-10 was likewise based on expert opinion and reviews of the literature. Experts from some 40 countries were involved in the project. A steering committee coordinated the activities of the different working groups, and the revision was finally put before and approved by a combined WHO/Adamha conference in 1985. For both DSM-IV and ICD-10, primary care versions are available, in which diagnostic criteria are simplified, several subtypes eliminated, and emphasis is placed on conditions encountered in everyday practice. Only in the case of ICD-10 was a version for researchers published, in which diagnostic criteria were defined in greater detail (DCR-10). Like the DSM, the ICD system has a multiaxial structure, but the axes differ in both publications.

Sustained efforts are being made to homogenize the two classification systems where possible. DSM is far more used in psychiatric research than the ICD system, which explains why the following analysis is DSM-oriented. Nevertheless, most of the considerations presented here are applicable to the ICD taxonomy as well.

Psychiatric diagnosing: past and present

Some 40 years ago, the framework of psychiatric diagnoses was profoundly different from the way it looks today. On the one hand we gained, on the other hand we lost.

Then, psychiatric diagnoses were chaotic, in that standardized and generally accepted diagnostic criteria were lacking. Without too much exaggeration one could claim that every "school" of some renown had established its own taxonomy. Hence diagnoses were poorly comparable. Methods to assess abnormal human behavior were nonexistent. This situation was rather disastrous for research, particularly biological research, dependent as it is on a precise and valid definition of the object of study. Diagnoses at that time were inaccurate, but refined, at least in Europe, due to the two dominant philosophies in psychiatry back in those days : phenomenology and psychoanalysis. In order to make a diagnosis, one was required:

- to provide a detailed account of the symptomatology of a given patient;
- to pay due attention to the experiential consequences of the symptoms;
- to describe in detail the psychogenesis of the disorder, ie, the alleged relationship between the complex: psychological development/personality structure/psychotraumatic event on the one hand, and the present psychopathology on the other.

In 1980, the third edition of the DSM appeared and the changes it brought about were profound. In a way they signified immense progress. A standardized and operationalized taxonomy was introduced that gained worldwide acceptance almost overnight by the psychiatric community, clinicians, and researchers alike.
However, the price that had to be paid for those benefits was high, in that the diagnostic process coarsened and markedly lost out in terms of sophistication, a statement that will be clarified in the next section.
Is this accusation a fair one? Can a classification system be blamed for shortcomings in the way we make a diagnosis? After all, classification of psychiatric disorders is, or rather ought to be, the end point of the diagnostic process, in which all data concerning symptomatology, causation, and course of a psychopathological condition crystallize in a single construct. In actual practice, however, classification is much more than that. To a considerable degree classification systems steer the diagnostic process. Psychopathological data tend to be viewed and interpreted in such a way as to fit as far as possible the diagnostic categories available.
The impact of classification on the diagnostic process is more profound the stricter and more detailed a taxonomic system spells out the diagnostic criteria. The influence that the DSM has exerted on the diagnostic process from the third edition onwards is a case in point.
Our trainees learn, as it were, to diagnose with a copy of the DSM in their hand or at least at the back of their mind. That which is not included in the DSM seems to have become almost irrelevant.
Since classification impacts on the making of a diagnosis, and since precise and valid diagnoses form the very bedrock of clinical psychopharmacology and biological psychiatry, classification has had and continues to have a profound influence on the development of those disciplines. Progress is slowed down if the definition of a diagnostic category is loose, if its validity is in doubt, or if available diagnostic categories do not fit clinical observations.
In the following sections, I shall endeavor to show to what extent the current diagnostic system has furthered or impeded progress. The group of mood disorders, in particular the construct of major depression, will be used as a paradigm, but the same reasoning can be applied to most of the diagnostic constructs currently distinguished.

Problems of validity

Predictive validity is the basic quality any diagnostic construct should possess. A diagnosis, once made, should allow reliable prognostication of symptoms, cause, course, outcome, and response to treatment. This is clearly not the case as far as the diagnostic construct of major depression is concerned:

- The diagnosis of major depression is based on evidencing X out of a series of Y *symptoms*, irrespective of which ones. This construct therefore encompasses a wide range of syndromes without providing any information on the type of depressive syndrome thus observed.
- Major depression can be precipitated by a variety of *etiological factors,* psychological, biological, or related to living conditions. In some instances, no precipitating factors are demonstrable.
- With regard to *pathophysiology*, current hypotheses postulate a causal role of serotonergic dysfunction and hypothalamo-pituitary-adrenocortical (HPA) axis disturbances. These have indeed been found to be associated with major depression in some patients, but not in others, without these patient subgroups coinciding with any of the currently distinguished depression subtypes. Furthermore, disturbances of these systems are not specific to depression, but occur in other diagnostic categories as well.[3,4]
- *Course and outcome* also fail to show a characteristic pattern.[5,6] Some patients only develop a single episode, whereas the majority of them experience several. One patient may recover completely, another will suffer from residual symptoms, and in another still chronicity will set in.[7-9]
- *Treatment response,* finally, is difficult to predict. Antidepressants may achieve complete recovery, partial response, or no response at all. Psychological interventions will be helpful in some patients, or totally useless in others.

The construct of major depression therefore shows great variability at almost every diagnostic level. Hence there is no question of any predictability being associated with the diagnostic characteristics: no single characteristic is reliably predictive of any other. In other words, the predictive validity of this construct is all but null.
Not only does the construct of major depression encompass a wide range of syndromes, but in the majority of cases it is also associated with other disorders, most notably personality and anxiety disorders.[10-13]

Thus it appears that major depression is not so much a diagnostic entity as a diagnostic multiplicity. What we have is an aggregate of disorders, which although they do share some symptoms, are by no means congruent and, in addition, differ in terms of course, outcome, treatment response, and, one has to assume, pathophysiology as well.

"Coarsening" of diagnosis

As mentioned above, over the past two decades diagnoses have become more reliable but less sophisticated. The reasons for this will now be clarified, taking the groups of mood disorders as a paradigm.

The eclipse of syndromal exactitude

Syndromal differentiation has disappeared from the diagnosis of depression. The major depression constructs distinguished by the DSM—major depression and dysthymia—cover a variety of syndromes. Moreover, the two lists of symptoms one can choose from are, for the most part, similar. Symptomatologically, the constructs resemble two unfocused and largely overlapping slides. I believe that this is detrimental to psychiatric research, particularly biological research. Study of the biological determinants of abnormal behavior requires above all precise definition of the object of study. It is highly unlikely that the search for the pathophysiology of vaguely defined constructs—unclearly demarcated from adjacent entities, probably being repositories for a variety of pathological conditions—stands much chance of success. Likewise, psychopharmacology is poorly served by the way depression is currently diagnosed. The syndromal heterogeneity of diagnostic constructs makes it impossible to demonstrate potential syndromal or symptomatological specificity of a given compound. Since a variety of new antidepressants are under development, several with high biological specificity and thus possibly higher psychopathological specificity than the drugs presently available, the current diagnostic system is a hindrance to psychopharmacological progress.

Do syndromes matter in biological psychiatry and psychopharmacology? They do indeed, and there is sufficient evidence to justify this statement. The syndrome of vital (or endogenous) depression, for instance, is a better candidate for tricyclic antidepressants than the syndrome of personal (or neurotic) depression.[14,15] Vital depression, moreover, is much less placebo-responsive than personal depression.[16] An example of syndromal importance for biological psychiatry is the concept of SeCA depression (stressor-precipitated, cortisol-induced, serotonin-related, anxiety/aggression-driven depression), which I recently introduced. It is a new (hypothetical) depression type characterized biologically by specific serotonergic dysfunctions and psychopathologically by disturbed regulation of anxiety and aggression, both of which are precursor symptoms of the depression and which are considered to be the core features of the depressive syndrome.[3]

Precise syndromal differentiation seems to me the indispensable counterpart of both biological and pharmacological research in psychiatry.

The comorbidity maze

Comorbidity is very widespread in psychiatry and seriously undermines the validity of research efforts.[17] For example, a depressed patient is included in a depression protocol and also qualifies for the diagnoses of generalized anxiety disorder with occasional panic attacks, alcoholism, and two or three personality disorders. A finding—biological, psychopharmacological, epidemiological, or otherwise—is made. Is this finding related to depression, to one of the other diagnoses, or to components of the syndromes covered by these diagnostic labels? Answers are not on hand. The problem is most often ignored, thus disqualifying most conclusions.

A sensible way to avoid the morass of comorbidity in experimental psychiatry and more particularly in biological psychiatry, is the strategy I have called *functionalization* of diagnoses.[18] Diagnosing in psychiatry is generally confined to two tiers: characterization of the prevailing syndrome(s), and a decision as to the best fitting categorical diagnosis or diagnoses. The diagnostic process in psychiatry can be widened using a third tier, that of functional psychopathology. This is achieved by dissecting the syndrome into what may be considered the elementary units of psychopathology, ie, the psychological dysfunctions underlying psychiatric symptoms. In a case of depression, for instance, these dysfunctions include disturbances in the regulation of mood, anxiety, and aggression, motoricity, information processing, memory, hedonic functioning, concentration, and others. Psychiatric symptoms are the manifestations of psychological dysfunctions. For example, hearing voices is a

symptom; a particular perceptual disturbance is the underlying psychological dysfunction. Functional analysis of a psychiatric syndrome is, thus, fundamentally different from symptom analysis.

"Functionalization" of psychiatric diagnoses is important for several reasons. First, the problem of comorbidly occurring disorders is bypassed (not resolved) by relinquishing the concept of discrete and separate disorders and studying primarily the biology and psychopharmacology of abnormally functioning psychological domains. Second, this approach provides insight into the functional abilities of the patient, ie, which psychological domains are deranged and which are still functioning within normal limits. Third, psychological dysfunctions are measurable, many of them quantitatively. This is in contrast to psychiatric syndromes or disorders, which permit, at best, a qualitative estimate of presence and severity. Functionalization is the obvious way to provide psychiatric diagnoses with a sound scientific foundation. If systematically carried through, functional psychopathology will ultimately lead to the equivalent of what pathophysiology is to somatic medicine: the discipline providing an understanding of the deflections in the psychological apparatus that underlie a particular psychiatric disorder.

Horizontal instead of vertical grouping of psychopathological phenomena

In present-day psychiatry, symptoms tend to be grouped horizontally, as if each carried equal diagnostic weight—we just count symptoms. Mood disorders are no exception to this rule. This approach resembles that of the internist who, in a case of pneumonia, would attach the same diagnostic valence to the symptom of fatigue as to the symptom of shortness of breath. In medicine, such an approach would be labeled malpractice. In psychiatry it is officially sanctioned.

A mental disorder can be considered as a composite of psychological dysfunctions, mutually interacting in a complex way. The diagnostic weight of the various components is presumably unequal. Some of them are primary, ie, the direct consequence of the underlying cerebral substratum; others are secondary, ie, derivatives of the pathophysiological processes. Primary symptoms should be the prime target of research into the biology of the disorder and of therapeutic interventions, given their availability.

Since the work of Eugen Bleuler, the fundamental distinction between primary and secondary symptoms has received hardly any attention. The reason is not difficult to guess: because there were no methods to study the brain, it was virtually impossible to validate the primary/secondary distinction. As a result of advances in biological psychiatry and psychopathology, that argument no longer holds good. Our studies in mood disorders are a case in point. They led us, as mentioned above, to the hypothesis that a subgroup of depression exists in which: (i) serotonergic functioning is demonstrably disturbed; (ii) anxiety and/or aggression dysregulation are the primary psychopathological features and mood-lowering the subsidiary ones; and (iii) serotonergic dysfunction and affective vulnerability are causally linked. If true, the proper treatment of such serotonin-related, anxiety/aggression-driven forms of depression would be a compound that ameliorates anxiety and/or aggression via regulation of serotonergic circuits.[3] Verticalization of psychiatric diagnoses could fundamentally change the strategy for developing novel psychopharmacological principles. Instead of finding drugs to fight disorders such as schizophrenia or major depression, the goal would shift towards the development of drugs that regulate core types of psychological dysfunction underlying a particular psychopathological state.

Verticalization studies presuppose careful dissection of the prevailing syndrome into its component parts: the psychological dysfunctions. This is another reason why the functional approach should be an integral part of making a psychiatric diagnosis.

Neglect of psychogenesis

A fundamental shortcoming of the prevailing psychiatric taxonomy is the lack of an etiological axis. The rationale for this is the wish to be atheoretical. With today's methodologies, however, it is possible to put forward an etiological hypothesis that is as reliable as any on the presence or absence and severity of particular psychopathological symptoms.

What is most particularly missing is the requirement to formulate a hypothesis on the relationship between axis I and axis II diagnoses. In this context, is the frequent co-occurrence of depression and the complex stressors/personality imperfections a mere coincidence or is it of causal significance in that the latter complex is the pacemaker of the depression? If a causal relationship is prob-

able, biological research into depression (or a particular type of depression) should focus primarily on the determinants of personality disorder rather than on those of depression.
This issue is of no less practical importance. If personality disorder constitutes the primary pathology, its treatment should be a integral part of the management of (certain types) of depression. Consequently, a refined diagnosis of depression should encompass diagnostic scrutiny of personality structure, its possible frailties, and the corresponding life events.
In summary, the practice of judging axes I, II, and IV independently ignores the possibility—probability even—that in depression these three domains broadly overlap, and does not lend itself to the formulation of hypotheses or the carrying out of corresponding research. In psychodynamic psychiatry, relationships between mood, personality, and life events are taken for granted. In experimental psychiatry, belief in the self-evident has been lost, but with the diagnostic approach that it champions, the remedy could become as serious as the disease.

Categories and clinical realities

Finally, the question should be raised as to what extent the multiplicity of available diagnoses adequately covers the real situation of the individuals who attend our clinics and therapeutic units.

Proliferation of diagnostic categories

From the third edition onwards, the DSM has standardized diagnoses and operationalized diagnostic criteria. Precise syndromal definition has been abandoned, and the diagnosis of depression is tied to a fixed number of symptoms from a given series, regardless of the actual symptoms. Various depression types are distinguished, not on the basis of symptoms, but on their severity and duration. Major depression is defined as severe (at least more severe than dysthymia), time-limited, and of at least 2 weeks' duration, while dysthymia is defined as a less severe, long-lasting mood anomaly. In this way, the DSM system creates "disorders," characterized by a compilation of nonsymptomatological and (crude) symptomatological criteria.
The dangers of this system are substantial. The number of symptoms necessary to qualify for a particular diagnosis has been determined arbitrarily. A considerable number of syndromes qualify for the same diagnosis. Moreover, much evidence indicates that the diagnostic constructs thus defined have little predictive validity as to their course, outcome, or treatment response.[14] For instance, major depression can occur once in a lifetime or be recurrent; it may remit completely or partially; antidepressants may be efficacious or inactive; and psychological interventions effective or to no avail.
The rigidity of the system and the discrepancies between diagnostic constructs and clinical realities have fueled the need for novel categories of depression. Thus, if instead of showing 5 out of the 9 symptoms listed under the heading major depression the patient has only 2 to 4, the diagnosis changes from major depression to subsyndromal depressive disorder.[19] Individuals with only one depressive syndrome are also included in depression studies, though to date they are so far diagnostically unclassified.[20] If the severity is less than that required for major depression and the duration less than that required for dysthymia, the diagnosis changes to minor depression. Severity criteria, however, are not specified. If episodes are recurrent and brief (less than 2 weeks), brief recurrent depression is diagnosed.[21] Brief episodes not rapidly recurrent have so far not received a categorical position. Entities such as those mentioned are currently studied epidemiologically, psychopharmacologically, and otherwise as if they were discrete and separable entities, or discrete and separable subforms of one overarching entity (see, for example, reference 22). Are those diagnostic constructs true categories, or artefacts generated by a diagnostic system based on nosological premises that prematurely and erroneously conceptualize diagnostic "packages," which, however, lack clinical relevance? This is still a moot question, but before accepting these packages as valid diagnoses, one should consider and exclude other explanations for the wide spectrum of mood disturbances encountered in clinical practice, besides the DSM-defined categories. I will briefly discuss three alternative explanations for nosological diversity that deserve serious scientific attention.

Worrying is mistaken for depression

People may go through difficult periods and may complain in the face of severe problems once in a lifetime, repeatedly, or chronically. At what point does worrying cease to be worrying and turn into depression? The

answer is not known. Psychiatry has failed to study these gray areas systematically. Hence the need to define ever more categories of mood anomalies, particularly with respect to milder forms. Boundary setting, however, is lacking. Is one symptom enough to qualify for the diagnosis of depression or are two enough or should there be a fixed minimum? Is symptom severity a critical feature, and, if so, how should it be defined: in terms of disruption of social and occupational life, decreasing work performance, subjective experience, or observer ratings? Is duration decisive and, if so, what should be the cutoff time? Due to the lack of answers, diagnostic categories have proliferated.

This state of affairs seriously undermines the validity of research data. How can we have confidence in the outcome of epidemiological studies if distress and depression are not clearly distinguishable, but are nevertheless distinguished? This is all the more relevant if the study has been carried out by lay interviewers, with only a brief training and without psychiatric experience, using highly structured, standard interviews of modest clinical sophistication and with only two answers allowed per question: affirmative or negative. I am alluding to instruments such as the Diagnostic Interview Schedule (DIS)[23] and the Composite International Diagnostic Interview (CIDI).[24] They have been used in several large-scale epidemiological studies, though poor agreement has been demonstrated between diagnoses based on interviews conducted by lay persons and diagnoses made by psychiatrists.[25,26]

How can one explore the biological determinants of depression or the clinical effects of antidepressants if the study group is composed of depressives and worriers? The pathological substrate of pneumonia and the efficacy of penicillin would not have been clarified if patients with pneumonia and those with a common cold had been confused.

Boundary problems should thus have high priority in depression research, but regretfully they have not. The fact that ever more depression categories are being proposed does not provide much solace.

Partial response is held to be a new depression type

It is generally held that in 60% to 70% of cases depression responds favorably to antidepressants, and this seems to be true for all types of antidepressants. Response to antidepressants is generally defined in terms of rating-scale scores. For instance, a reduction in the Hamilton score of at least 50% identifies someone as a responder. However, more often than not, symptoms attenuate, but do not disappear, or some symptoms disappear but others persist.[27] This might have led to proposals for new, so-called subsyndromal depression categories.

Another diagnostic riposte to partial response (a euphemism for partial failure) is the postulate of two depression types occurring together, one responding to the prescribed antidepressant while the other one does not. I am alluding to the concept of double depression, ie, major depression superimposed on dysthymia.[22] Symptomatologically, however, major depression and dysthymia are virtually indistinguishable, differing principally only in severity and duration. How then can one decide whether residual depressive symptoms are the remnants of major depression or continuing dysthymia? Incomplete response is, I believe, a more plausible explanation for residual symptoms than the assumption of new depression types, especially since those novel constructs have, in no time, become the subject of study in their own right.

Unsuitability of nosology for ordering mental pathology

Since its inception as a scientific discipline by Kraepelin, psychiatry has been wedded to nosology as the classificatory principle of mental pathology. Research in psychiatry is disorder-oriented, particularly in biological psychiatry, where the search for markers and possible causes of true disorders, like schizophrenia, major depression, or panic disorder is the major goal. As I have argued elsewhere, abnormal psychic states can be conceived of in a different way, ie, as reaction patterns to noxious stimuli.[28] Noxious stimuli will disturb a variety of neuronal circuits and, hence, a variety of psychological systems. The extent to which neuronal disruption will be induced by a noxious stimulus is variable, because it is influenced by personality strength and neuronal adaptability. Psychiatric conditions will therefore lack symptomatological consistency and predictability. For instance, mood lowering is blended with fluctuating measures of anxiety, anger, obsessional thoughts, addictive behavior, cognitive impairment, and psychotic features. These features will vary in intensity and prominence between subjects and, over time, within the same individual. The need to demarcate

depression categories is thus never-ending and in essence futile.
The reaction-form model provides an explanation for several other urgent questions facing psychiatry. First, the question as to why most psychiatric patients seem to suffer from a multitude of disorders. According to this model, the co-occurrence of various discrete mental disorders is mainly appearance. In fact, we are dealing with ever-changing composites of psychopathological features. Secondly, the reaction-form model offers an explanation for why, in spite of more than 35 years of intense efforts, no biological markers of categorical entities have been established, whereas the search for correlations between psychological and biological dysfunctions has been quite successful.
The reaction-form model, if valid, would have profound consequences for biological psychiatry. The search for markers and, eventually, causes of discrete mental disorders would be largely futile. The most one could do would be to group the multitude of reaction patterns in a limited number of diagnostic "basins," such as the group of the psychotic, demential, and affective reaction forms, each of which, however, would show considerable heterogeneity. Just as it is futile to search for the antecedents and characteristics of, for example, the group of abdominal disorders, so it would equally be foolhardy to hope for the discovery of, eg, the pathophysiology of the "basin" of affective reaction forms. Within the scope of this model, the focus of biological psychiatric research has to shift from the alleged mental "disorders" to disordered psychological domains. It is not schizophrenia, panic disorder, or major depression as such that will be studied, but disturbances in perception, information processing, mood regulation, anxiety regulation, and impulse control, to name but a few. A biology of psychological dysfunctions as they occur in dysfunctional mental states would thus be the ultimate goal of biological psychiatric research. Adopting the three-tier diagnostic approach in psychiatry (adding the "functional" level) would offer the opportunity to explore the relative merits of both diagnostic viewpoints—the nosological and the reaction-form model—for experimental psychiatry.

Discussion

Depression research

Before the publication of the third edition of the DSM, the diagnosis of depression was weak in that terminology was not standardized and criteria were not operationalized, but it was strong in that symptomatological analysis was refined (at least in Europe, where phenomenology was in vogue) and etiological analysis prominent (particularly psychogenesis, officered by psychodynamic thinking). At the current time, the diagnosis of depression is strong in that standards are systematized and defined, but is weak in that syndromal specification has been relinquished and axis I, II, and IV data are left unconnected.
Research, and particularly biological research, is greatly hampered by these shortcomings. The depression constructs we study are symptomatologically ill-defined and heterogenous. It is unlikely that they can be considered as "entities" whose features such as biology, genetics, epidemiology, or treatment responses can be properly studied. Moreover, clinical practice indicates that depression, (some) personality deviations, and stressor susceptibility are so tightly interwoven that a hypothesis about their possible interrelationship seems indispensable, not only in terms of treatment, but for the sake of research as well. If it was shown to be plausible that (certain types of) depression (are) is the consequence of personality frailties and corresponding life events, research into the origin of depression would have to shift from depression per se to the underlying personality disorder.

Overlap of disorders

What severely hampers depression research is the fact that depression rarely occurs in isolation. The overlap between mood, anxiety, and personality disorders is so fundamental that discussion of any depression study should include whether the observed phenomena relate to depression, to coexisting anxiety or personality disorders, or to components of these conditions. Generally, this question is carefully avoided—avoidance behavior, however, does not promote progress.

Horizontal vs vertical approach

The diagnosis of depression has regressed to a horizontal level. Symptoms are simply counted, and if a certain number from a given series are present, depression is considered to exist. The essence of making a diagnosis, however, involves a vertical approach ranking symptoms according to their relationship to the pathophysiological substratum underlying a particular psychopatho-

logical condition. Symptoms directly related to the substratum should be the prime target of treatment efforts and pathogenetic research.
A prerequisite for the verticalization of diagnosis is functionalization of diagnosis, ie, dissection of the prevailing syndrome(s) into its (their) component parts—in other words, a series of psychological dysfunctions. Those dysfunctions should be charted and measured, whenever possible quantitavely. Functionalization of diagnoses would raise psychopathology to a true scientific level.

New diagnostic categories

Present-day psychiatric taxonomy is based on nosological premises. Mental disorders are considered as discrete entities. For the diagnosis of depression, this philosophy has acted as a straitjacket, for two reasons. First, many mood disorders could not be accommodated in the available categories, and second, the boundary between distress and depression appeared hard to identify. Consequently, there was a need to propose ever more new depression categories, each viewed as an entity in its own right and studied as such. Validity research has, however, not kept pace. This is why this "nosologomania"[29] has brought about a strong inflationary trend in depression diagnosis. Moreover, the proliferation of ever more diagnostic categories has magnified the problems caused by comorbidity.

Validity of the nosological disease model

The considerable overlap between mood, anxiety, and (certain) personality disorders raises a question of a fundamental nature, that of the validity of the nosological disease model for depression diagnosis. Can the pathology of affect regulation indeed be subdivided into discrete entities, or is an alternative disease model, ie, the reaction-form model, more appropriate and of greater heuristic value? According to the latter model, affect pathology does not crystallize into discrete "packages," but manifests itself in inter- and intra-individually ever-changing combinations of mood, anxiety, and aggression pathologies. This model provides answers for burning questions where the nosological model remains silent. Why do most patients with affective pathologies qualify for a host of disorders? Why, after searching for more than 35 years, has not a single biological marker for any disease entity been found?
The answer, according to the reaction-form model, is that the so-called "disorders" are artefacts of a categorical classification philosophy and not real disease entities. Disordered psychological domains (and in particular those that are directly correlated with the brain dysfunction underlying a particular state of psychological disorganization) should take center stage in biological psychiatry and psychopharmacology. Functional psychopharmacology, ie, treatment of psychological dysfunctions rather than (pseudo)disorders would be the "therapeutic arm" of the reaction-form disease model.
The heuristic value of the reaction-form model is such that it should be studied comparatively as a possible counterpart to the nosological model.[29]

Guidelines for diagnosis of depression

To avoid the pitfalls discussed here, the diagnosis of depression has to be based on the following pillars: (i) refined syndromal characterization; (ii) introduction of a third (functional) tier in the diagnostic process; (iii) formulation of hypotheses regarding the relation between axis I and II diagnoses; and (iv) systematic study of the "vertical position" of the various psychological dysfunctions constituting the depressive syndrome.

Conclusion

The present discussion has focused on the diagnosis of depression. Much of what has been said is valid for psychiatric diagnoses in general. Hence I believe that serious investigation of the very foundations of our discipline, ie, diagnosis, is indicated.[4] ❑

Based on lectures given at the Congress of the Association of European Psychiatrists held in Copenhagen, September 20-25, 1998 and at the Annual Meeting of the Royal Australian and New Zealand College of Psychiatrists, Christchurch, New Zealand, September 3-7, 1997.

El impacto de la clasificación en la psicofarmacología y en la psiquiatría biológica

La clasificación nosológica en psiquiatría, tal como se aplica actualmente, no facilita la investigación biológica ni psicofarmacológica.

- *La precisión sindromática ha desaparecido. Por consecuencia, es imposible determinar: a) si un fármaco dado afecta una configuración sintomática específica, b) cuán exacta es la correlación entre una conducta y un trastorno biológico determinado. El problema de los diagnósticos imprecisos está aumentado por el fenómeno de la comorbilidad.*
- *El límite entre distrés y trastorno está mal definido.*
- *La configuración sintomática y ciertas variables no sintomatológicas como duración y gravedad se relacionan prematuramente con el fin de conceptualizar categorías nosológicas. La validez de estos constructos no se ha demostrado suficientemente. Esto destruye la validez de los estudios biológicos y conduce a una "nosologomanía", es decir, a una serie siempre creciente de "trastornos" psiquiátricos subvalidados.*
- *Los síntomas se agrupan de manera horizontal como como si todos ellos tuvieran la misma "valencia" diagnóstica, lo que parece muy poco probable.*
- *El modelo nosológico de enfermedad se acepta incondicionalmente y con escasas críticas. Se ignoran los modelos alternativos, especialmente el modelo de tipo reaccional, a pesar que posee un gran valor heurístico y por lo tanto merece ser bien explorado.*

En este artículo se proponen estrategias (de investigación) para remediar esta situación.

Impact de la classification sur la psychopharmacologie et la psychiatrie biologique

La classification nosologique en psychiatrie, telle qu'elle est actuellement utilisée, ne facilite pas la recherche biologique et psychopharmacologique.

- *L'acuité du syndrome n'existe plus. Par conséquent, il est impossible de déterminer : a) si un type particulier de médicament influe sur une configuration symptomatique particulière; b) quelle est la manifestation comportementale exacte d'un trouble biologique particulier. Le problème de l'imprécision diagnostique est considérablement amplifié par le concept de comorbidité.*
- *La limite entre souffrance et maladie est mal définie.*
- *La configuration des symptômes et certaines variables non symptomatiques telles que la durée et la sévérité sont liées de façon prématurée afin de conceptualiser des entités catégorielles. La validité de ces entités n'a pas été suffisamment démontrée. Ceci affaiblit la validité des études biologiques et conduit à une "nosologimanie", c'est-à-dire, une série toujours en augmentation de "troubles" psychiatriques sous-validés.*
- *Les symptômes sont groupés de façon horizontale comme s'ils avaient tous la même "valence" diagnostique, ce qui est, néanmoins, très improbable.*
- *Le modèle nosologique de la maladie est accepté de façon inconditionnelle et sans critique. Les modèles alternatifs ne sont pas pris en compte, en particulier le modèle "forme réactionnelle", bien qu'il ait une valeur heuristique considérable et mérite d'être examiné rigoureusement.*

Des stratégies (de recherche) pour remédier à cette situation sont énumérées.

REFERENCES

1. Kahlbaum K. *Die Gruppierung der Psychischen Krankheiten [The Grouping of Mental Diseases].* Danzig, Poland: Kafemann; 1863.

2. Feighner JP, Robins E, Guze SB, Woodruff RA Jr , Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry.* 1972;25:57-63.

3. van Praag HM. Faulty cortisol/serotonin interplay. Psychopathological and biological characterisation of a new hypothetical depression subtype (SeCA depression). *Psychiatry Res.* 1996;65:143-157.

4. van Praag HM. Over the mainstream: diagnostic requirements for biological psychiatric research. *Psychiatry Res.* 1997;72:201-212.

5. Hagnell O. Affective diseases—their course in a longitudinal perspective: the Lundby study. *Psychiatrie Psychobiol.* 1989;4:275-285.

6. Angst J, Preizig MD. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients: results of a prospective study from 1959 to 1985. *Arch Neurol Psychiatry.* 1995;146:5-16.

7. Surtees PG, Barckley C. Future imperfect: the long-term outcome of depression. *Br J Psychiatry.* 1994;164:327-341.

8. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity and levels of psychopathology in major depression. *Arch Gen Psychiatry.* 1992;49:809-816.

9. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry.* 1999;156:1000-1006.

10. Black DW, Bells S, Hulbert J, Rasrallak A. The importance of axis II in patients with major depression: a controlled study. *J Affect Disord.* 1988;14:115-122.

11. Ormel J, Tiemens B. Depression in primary care. In: Honig A, van Praag HM, eds. *Depression, Neurobiological, Psychopathological and Therapeutic Advances.* Chichester, UK: John Wiley; 1997.

12. Griez E, Overbeek T. Comorbidity of depression and anxiety. In: Honig A, van Praag HM, eds. *Depression, Neurobiological, Psychopathological and Therapeutic Advances.* Chichester, UK: John Wiley; 1997.

13. Hirschfeld RMA, Shea MT, Holzer CE III. Personality dysfunction and depression. In: Honig A, van Praag HM, eds. *Depression, Neurobiological, Psychopathological and Therapeutic Advances.* Chichester, UK: John Wiley; 1997.

14. van Praag HM. Diagnosing depression. Looking backward into the future. *Psychiatr Dev.* 1989;7:375-394.

15. Rush AJ, Weissenburger JE. Melancholic symptom features and DSM-IV. *Am J Psychiatry.* 1994;151:489-498.

16. Fairchild CJ, Rush AJ, Vasavada N, Giles DE, Khatami M. Which depressions respond to placebo? *Psychiatry Res.* 1986;18:217-226.

17. van Praag HM. comorbidity (psycho-)analyzed. *Br J Psychiatry.* 1996;168:129-134.

18. van Praag HM. Two-tier diagnosing in psychiatry. *Psychiatry Res.* 1990;34:1-11.

19. Sherbourne CD, Wells KB, Hays RD, Rogers W, Burnam MA, Judd LL. Subthreshold depression and depressive disorder: clinical characteristics of general medical and mental health specialty outpatients. *Am J Psychiatry.* 1994;151:1777-1784.

20. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *J Affect Disord.* 1997;45:5-18.

21. Angst J, Merikangas KR, Scheidegger P, Wicki W. Recurrent brief depression: a new subtype of affective disorder. *J Affect Disord.* 1990;19:37-38.

22. Keller MB, Hirschfeld RMA, Hanks D. Double depression: a distinctive subtype of unipolar depression. *J Affect Disord.* 1997;45:65-73.

23. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. *Arch Gen Psychiatry.* 1981;38:381-389.

24. Robins LN, Wing JK, Wittchen HU, et al. The Composite International Diagnostic Interview: an epidemiological instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatry.* 1988;45:1069-1077.

25. Anthony JC, Folstein M, Romanowski AJ, et al. Comparison of the lay diagnostic interview schedule and a standardized psychiatric diagnosis. *Arch Gen Psychiatry.* 1985;42:667-675.

26. Helzer JE, Robins LN, McEvoy LT, et al. A comparison of clinical and diagnostic interview schedule diagnoses. *Arch Gen Psychiatry.* 1985;42:657-666.

27. Fava GA. The concept of recovery in affective disorders. *Psychosother Psychosom.* 1996;65:2-13.

28. van Praag HM. Make Believes in Psychiatry or the Perils of Progress. New York, NY: Brunner Mazel; 1992

29. van Praag HM. Concerns about depression. *Eur Psychiatry.* 1995;10:269-275.

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In 1999, for the first time, the World Psychiatric Association has awarded the Jean Delay prize. This prize is intended as a reward for contributions that forge links between clinical, biological, and social aspects of psychiatry, or between psychotherapy and pharmacotherapy.

The international jury, under the presidency of Prof Norman Sartorius, has selected ***Sir David Paul Goldberg,*** who was awarded a prize of $40000 ***during the opening ceremony of the XIth World Congress of Psychiatry*** (Hamburg, Germany, August 6-11,1999).

The next Jean Delay prize will be awarded during the XIIth World Congress of Psychiatry (Yokohama, Japan, August 2002). Applications or nominations of applicants, including a cover letter and a description of the work presented, should be sent to:

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Conceptualization of the liability for schizophrenia: clinical implications

Ming T. Tsuang, MD, PhD, DSc; FRCPsych; William S. Stone, PhD; Stephen V. Faraone, PhD

Ming T. TSUANG

Although substantial progress has been achieved in both the diagnosis and treatment of schizophrenia and the understanding of its neurobiological substrates, a full understanding of its origins and pathogenic mechanisms remains elusive. Understanding the development of schizophrenia is critical for developing new treatment strategies, in part because early interventions—ie, secondary prevention—are associated with better treatment outcomes. There is thus a growing emphasis on the accurate diagnosis of schizophrenia as soon as symptoms of psychosis are evident. Conceptually, of course, the most effective treatment would involve the prevention of psychosis altogether—ie, primary prevention.

Progress towards this goal, however, remains in its infancy, in part because we are only just learning to identify what the genetic liability to schizophrenia looks like before the onset of psychosis. In this paper, we discuss recent progress in this area by focusing on "schizotaxia," a clinically meaningful condition that may reflect the liability for schizophrenia. We then consider an important implication of identifying this condition: the possibility of treatment strategies for the primary pre-

Historically, the Diagnostic and Statistical Manual of Mental Disorders *(DSM) diagnostic criteria for schizophrenia have emphasized several features, including symptoms of psychosis, a dissociation of symptoms from their etiology, a reliance on clinical symptoms, and a categorical approach to classifying the disorder. Although these emphases are quite useful, they have limitations. We review these here, and stress the importance of incorporating recent data on the genetic / biological and neurodevelopmental origins of schizophrenia into current conceptions of the disorder. We also review "schizotaxia," which is a concept that embodies this point of view, occurs before the onset of psychosis, and is hypothesized to represent the liability for schizophrenia. If our hypothesis on this point is correct, the identification of schizotaxic individuals will eventually facilitate the development of prevention strategies by identifying a premorbid (but clinically significant) condition for schizophrenia. Moreover, the identification of biological or neuropsychological components of schizotaxia will provide more specific bases for developing novel treatment interventions. Our initial attempts to develop protocols for the assessment and treatment of schizotaxia are encouraging, and will be reviewed.*

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vention of schizophrenia. The development of the notion of schizotaxia, however, begins with a review of how schizophrenia has been classified over the last century, especially in regard to the diagnostic emphasis on symptoms of psychosis, the view of schizophrenia as a discrete category, and the dissociation of clinical symptoms from their underlying genetic/biological etiologies. Limitations of these approaches are then considered, followed by ways in which genetic research has helped to focus attention on phenotypic expressions of schizophrenia genes (ie, schizotaxia) before the onset of psychosis. Finally, clinical implications of schizotaxia are considered.

The classification of schizophrenia: historical background

In 1895, Kraepelin distinguished dementia praecox from manic-depressive psychoses.[1] Dementia praecox referred to patients with global disruptions of perceptual and cognitive processes *(dementia)*, and early onsets *(praecox)*. These patients usually showed an onset in early adulthood, and a progressively deteriorating course that did not include a return to premorbid levels of function. In contrast, manic-depressive features included relatively intact thinking, a later onset, and an episodic course in which episodes of psychopathology alternated with periods of normal function.

Eugen Bleuler used Kraepelin's systematic classification of psychoses and a theoretical model of etiological processes to reformulate dementia praecox as "schizophrenia," from the Greek words for "splitting of the mind."[2] His reasoning was that the defects in thinking in schizophrenia were not identical to those occurring in dementias associated with aging, for example, but instead reflected deficits of "association." Bleuler described four basic symptoms: ambivalence, disturbance of association, disturbance of affect, and a preference for fantasy over reality. To Bleuler, these reflected schizophrenia's fundamental defect: the disassociation or splitting of the normally integrated functions that coordinate thought, affect, and behavior. It is important to note that, in contrast to subsequent *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, Bleuler's diagnosis of schizophrenia did not depend on psychotic features such as hallucinations and delusions.

Bleuler's emphasis on theory as a means for determining the diagnostic relevance of signs and symptoms contrasted sharply with Kraepelin's reliance on empirical observations. Bleuler's approach was also notable for other reasons. First, his reformulation of dementia praecox as "the group of schizophrenias" foreshadowed the modern view that schizophrenia is a heterogeneous group of disorders with similar clinical presentations. Second, Bleuler included defects in affect as a core feature of the disorder. Third, his view of schizophrenia allowed for the possibility of remission or recovery.

Kraepelin's and Bleuler's observations provided the foundation for contemporary systems of psychiatric classification, including the *International Classification of Disease and Death* (ICD) and the American Psychiatric Association's DSM. These systems have thus benefited from incisive clinical observations of, and conceptualizations about, schizophrenic illness. They also, however, inherited the limitations of Kraepelin and Bleuler's efforts at classification and diagnosis. The first DSM definition of schizophrenia was vague, unreliable, and allowed for too much discretion on the part of clinicians. As a result, apparent geographical differences arose in the rates of schizophrenia. In the United States, schizophrenia became the diagnosis of choice for psychotic conditions that lacked a clear "organic" etiology, and thus appeared to occur more frequently than it did in the United Kingdom.[3] DSM-II continued the DSM-I tradition of unreliable diagnoses, although it did incorporate the issue of differential diagnoses. Both of these early systems viewed psychosis as a key feature of the disorder (we use the term psychosis to encompass hallucinations, delusions, and gross disorganization of thought or behavior). Interestingly, however, and despite its emphasis on psychosis, DSM-II did contain a nonpsychotic subtype of schizophrenia, called latent schizophrenia, which included a heterogeneous group of patients who in DSM-I were diagnosed with "incipient" or "borderline" schizophrenia, among other conditions. As the term "latent" implies, however, the category was intended to encompass individuals with underlying or occult psychotic conditions, instead of identifying individuals who had schizophrenia in the absence of psychosis. Nevertheless, the category did represent an important attempt to delineate the role of psychosis in schizophrenia.

DSM-III resulted largely from the efforts of the "neo-Kraepelinian" movement of the 1960s and 1970s,[4] and from the efforts of other investigators in psychiatry and clinical psychology who argued for empirical, psychometric validation of psychiatric syndromes (eg, reference 5).

DSM-III represented a marked shift from previous DSMs, and contained a number of innovations, like field tests of diagnostic reliability, specific inclusion and exclusion criteria for diagnoses, multiaxial diagnosis, and a focus on the description of syndromes and course of disorders rather than inferences about their etiology. This latter point made psychiatric diagnosis more explicitly consistent with the diagnosis of other medical disorders of uncertain etiology.[6,7]

DSM-III's use of clearly defined criteria narrowed the construct of schizophrenia and in so doing improved its diagnostic reliability. This improved the clinical homogeneity of the disorder and facilitated its delineation from other serious mental illnesses. Still, DSM-III retained the position that psychosis was fundamental to the definition of schizophrenia, as Criterion "A" required an hallucination or delusion at some point in the illness. Similarly, Criterion A in DSM-III-R required "characteristic psychotic symptoms." In the latter revision, the type of psychotic symptoms required for the diagnosis was broadened to include gross behavioral disorganization (eg, incoherence, catatonia, and grossly inappropriate affect), although types of hallucinations or delusions, by themselves, sufficed to meet the Criterion.

In DSM-IV, Criterion A could be met through a combination of delusions, hallucinations, and gross disorganization (of speech and/or behavior). Because 4 out of 5 symptoms are related to psychosis (negative symptoms are the 5th symptom in the category), and Criterion A requires at least 2 out of 5 symptoms, psychosis remains necessary for the diagnosis of schizophrenia. Moreover, delusions alone are enough to satisfy the Criterion if they are bizarre, as are hallucinations, if they involve one or more voices engaging in running commentary or ongoing conversation. Thus, recent changes in DSM criteria have expanded the nature of the psychotic symptoms required for diagnosis, but have retained the emphasis on psychosis in the construct of schizophrenia.

Although the evolution of the DSM is emphasized here to trace the importance of psychosis in diagnostic classifications of schizophrenia, symptoms of psychosis—especially delusions and hallucinations—are also core features of ICD diagnostic criteria. The ICD-10 diagnosis of schizophrenia, for example, is heavily influenced by the Schneiderian concept of "nuclear" schizophrenia, which involves First-Rank Symptoms. As is well known, these symptoms center on types of delusions and hallucinations.[8]

Limitations of the current view of schizophrenia

It is now generally agreed that stringent, narrow diagnostic criteria for schizophrenia and other mental disorders were needed in the 1970s and 1980s to improve the reliability of clinical diagnoses. They were also needed to counteract the prevailing view that mental illnesses were "myths" that harmed patients by stigmatizing them with damaging diagnostic labels. Periodic revisions of the major classificatory systems have refined diagnoses further, increased their reliability, facilitated the task of differential diagnosis, and provided the basis for empirical methods to determine which symptoms most appropriately characterized specific disorders. Consequently, communications about, and diagnoses of, mental disorders are far more standardized among mental health professionals and other interested parties than they used to be, and the rationales for specific diagnostic criteria are much clearer. The reliability of diagnosis provided by recent DSMs has also benefited research to the extent that the clinical characteristics of samples are more standardized across studies and thus are more easily replicated. Moreover, the use of stringent diagnostic criteria laid the groundwork for studies to assess the validity of the concept. In fact, the "modern" view of schizophrenia (DSM-III and later) also has diagnostic validity. It can be delineated from other disorders; for example, it shows familial loading, and it predicts outcome (greater levels of functional impairment predict larger numbers of recurrent episodes).

Despite the many advances of DSM-III and its successors, however, we may still consider how the classification of schizophrenia could be improved further. This is not intended as a criticism of our progress thus far, but instead reflects the need to modify our conceptual and classificatory schemes as new information becomes available. In this context, at least three limitations of the current diagnostic criteria may be addressed, including: its emphasis on psychosis, its definition of schizophrenia as a discrete category, and its dissociation of symptoms from their etiology. Each of these limitations leads to the same issues: can the validity of the diagnostic criteria for schizophrenia be increased while its reliability is retained? More specifically, is the current classification of schizophrenia the most accurate reflection available of the biological condition that pro-

duces it? Perhaps most importantly from a practical point of view, would alternative conceptions of schizophrenia promote the development of novel treatment strategies? We address these issues, first, by revisiting the issue of psychosis.

Psychosis and the definition of schizophrenia

As the previous discussion of DSM diagnostic criteria emphasized, psychosis has long been the sine qua non for schizophrenia. But is psychosis really a specific component of schizophrenia, or is it more of a nonspecific indicator of severe mental illness? A variety of evidence supports the latter view. It is clear that psychosis is neither specific to schizophrenia, nor even to psychiatric disorders. It occurs, for example, in neurological disease (eg, Alzheimer disease, Huntington disease, schizophrenia-like psychosis of epilepsy, vascular dementia, and traumatic brain injury) and can be caused by a range of toxic substances or impaired metabolic states. Even Schneiderian first-rank symptoms, which have played such a prominent role in defining the nature of psychotic symptoms in modern diagnostic systems, are not specific to schizophrenia.[9] Similarly, several recent factor-analytic studies showed that measures of psychosis in schizophrenia did not differentiate it from other forms of psychopathology.[10,11]

Bell et al,[12] for example, showed that duration of illness and exclusion of affective symptoms correctly classified 97% of first-episode psychosis patients as having DSM-III-R schizophrenia, and also correctly identified 97% of such patients who did not have schizophrenia. The inclusion of DSM-III-R's psychosis criterion (Criterion A) was not necessary to achieve these levels of sensitivity and specificity, nor did they improve the prediction. Serretti et al[13] obtained a 4-factor solution for items on the Operational Criteria Checklist for Psychotic Illness among a large sample of DSM-III-R inpatients having either schizophrenia or a mood disorder. Although they found that two of their factors were more closely related to affective disorders and two were more related to schizophrenia, the psychopathology of subjects with schizophrenia overlapped that of bipolar patients on a "disorganization" factor. Psychotic symptoms among other diagnostic groups have also been noted,[14,15] although the issue remains controversial (eg, reference 16).

Notably, several molecular genetic studies failed to find linkage to schizophrenia on the basis of the DSM diagnosis, but instead showed stronger evidence for linkage when the phenotype was broadened to include additional psychotic disorders (eg, Maziade et al[17] at chromosome 6p and Wildenauer et al[18] at chromosome 18p). Results from other genetic studies have also added to converging evidence that different psychotic disorders share common elements.[19] For example, at least one disorder in the schizophrenia spectrum—schizoaffective disorder—might belong to an affective disorder spectrum as well.[19,20] Consistent with this view, schizoaffective disorder occurs in families with either schizophrenia or affective disorders. More generally, both schizophrenia and affective disorders occur at elevated rates in families with either disorder (eg, reference 21). Moreover, evidence for genetic linkage for both types of psychotic disorder has been obtained at similar chromosomal loci. Ginns et al,[22] for example, obtained evidence for linkage at 6p for bipolar disorder in Old Order Amish pedigrees, near the same region that Maziade et al, and others, have identified.[23] Similarly, the chromosome 10p region was implicated for both schizophrenia and bipolar disorder in the National Institute of Mental Health (NIMH) Genetics Initiative pedigrees,[24-26] and regions in 13q and 18p were also implicated recently in both of these disorders.[19]

One rationale for the similarities between psychotic symptoms in different disorders may involve inherent pathophysiological effects of psychosis. Several lines of evidence support this possibility. One stems from observations that clinical outcomes of schizophrenia improve when treatment is obtained early in the illness.[27] Another involves the growing body of evidence that some patients with schizophrenia show neurobiological abnormalities, such as enlarged ventricles, loss of tissue volume, degeneration of membrane phospholipids, and/or delayed P300 waves in event-related potential paradigms.[28] Recently, evidence consistent with the possibility of common neurobiological mechanisms across psychotic conditions has emerged, involving, for example, abnormal γ-aminobutyric acid (GABA)-ergic neurotransmission.[29]

Thus, similarities in psychotic symptoms in different disorders may be apparent at multiple genetic and (other) biological levels, as well as phenomenologically. What are the implications of such similarities? Crow proposed a continuum of psychosis that crosses diagnostic boundaries,[30-32] and suggested that schizophrenia, schizoaffective disorder, and affective illness exist along one or

more such continua. While he accepted the view that prototypical entities corresponded to schizophrenia and affective illness, he rejected the idea that they had distinct etiologies. Instead, he hypothesized that natural variation along one or more dimensions produced the prototypical disorders. He postulated that a common genetic deficit, located in the pseudoautosomal region of the sex chromosomes, was shared by psychotic disorders, and hypothesized further that genes related to psychosis were responsible for cerebral dominance and the localization of language.

Support for the pseudoautosomal hypothesis is weak,[33-35] and a psychosis gene shared by all psychotic disorders has yet to be discovered. Nevertheless, Crow's view of psychosis is intriguing. If, in fact, psychosis has an etiology apart from other core symptoms of schizophrenia, then the DSM's diagnostic focus on psychosis in schizophrenia could be a mistake. In the hunt for the causes of schizophrenia, psychosis could be a red herring.

The foregoing discussion of common elements in psychoses is consistent with Crow's notion of a continuum of psychosis, in regard to its common phenomenology and etiology. It differs from Crow's view, however, in its implications for the construct of schizophrenia. Similarities between psychotic states do not necessarily imply that the underlying disorders lie on the same continuum. An alternative view is that since psychotic states may impair functioning in a relatively global manner, and may have adverse neuropathological effects of their own, their net effect may be to emphasize superficial similarities between such disorders, while obscuring more subtle, but defining, differences between them.

In summary, we see two problems with the use of psychosis as a sine qua non for schizophrenia. First, mounting evidence suggests psychosis may be the "fever" of severe mental illness. While it is a serious problem, it is a nonspecific indicator. Second, psychosis is an end-state condition that, in comparison with other indicators, is a relatively distant consequence of schizophrenia's causes and pathophysiology. If these views are correct, then the focus on psychosis may actually hinder progress in searching for the causes of schizophrenia. In the next two sections, we discuss additional limitations of the diagnostic focus on psychosis, and consider alternative conceptualizations of schizophrenic illness.

DSM-IV schizophrenia is a discrete category

Like other disorders, DSM-IV defines schizophrenia as a discrete category rather than a quantitative dimension, despite its qualification that "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" *(p xxii, DSM-IV)*.

An implicit implication of this approach is that schizophrenia differs qualitatively from states of health or normalcy. This idea holds that schizophrenia begins with the onset of its symptoms as listed in DSM-IV. Before that time, the disorder cannot be recognized validly; if the criteria for other disorders are also not met, individuals cannot receive any psychiatric diagnoses. To a significant degree, the "cut point" for making the decision is whether psychotic symptoms are present or not.

In general, a reliance on discrete categories raises potential problems for cases that share symptoms of multiple disorders, because they may lead to artificial boundary categories and elevated rates of comorbidity.[36] Certainly, dimensional models of psychopathology have conceptual and pragmatic limitations as well.[37] For example, although a variety of studies have identified underlying dimensions of the diagnostic criteria for schizophrenia, (eg, positive, negative, and disorganized symptoms), both the number and the content of these dimensions remain unclear.[38] These concerns are significant, but the question remains as to whether a dimensional model describes the biological nature of schizophrenia more accurately than a categorical one? Is it more valid?

Certainly, a dimensional view of schizophrenia is more consistent (than a categorical one) with polygenic models of inheritance, which is the model that provides the best account of the familial transmission of schizophrenia.[23,39] Polygenic models assume that multiple genes combine with one another and with environmental factors to cause schizophrenia. Because multiple genes and environmental risk factors are involved, it is possible for people to have low, moderate, or high "doses" of risk factors that predispose to schizophrenia. People with very high doses are at high risk for schizophrenia, those with moderate doses may have related conditions such as schizotypal personality disorder, negative symptoms, neuropsychological impairment, or other neurobiological manifestations of the predisposition to schiz-

ophrenia.[40] It is clear that, in this view, a dimensional model describes the range of schizophrenic illness better than does a categorical one.

In fact, a partial foundation for a dimensional view of the biological/clinical manifestations of the vulnerability to schizophrenia already exists in the body of research about "schizotaxia," a term originally introduced by Meehl[41] to describe the unexpressed genetic predisposition to schizophrenia. Meehl suggested that individuals with schizotaxia would develop either schizotypy or schizophrenia, depending on the protection or liability afforded by environmental circumstances, although he later proposed that schizotaxia need not progress into either of these more overt conditions.[42] Given current data showing that, in addition to genes, environmental events (eg, obstetric complications, viruses) augment susceptibility to schizophrenia, Faraone et al[43] proposed that we use the term schizotaxia to indicate the premorbid, neurobiological substrate of schizophrenia.

Now, almost 40 years after the idea of schizotaxia was first advanced, a preponderance of evidence shows it to be a clinically meaningful condition. In fact, studies of nonschizotypal, nonpsychotic relatives of schizophrenic patients show that schizotaxia is not merely a theoretical construct, but has distinct psychiatric and neurobiological features. These include negative symptoms, neuropsychological impairment, impaired eye-tracking, and structural brain abnormalities.[43]

Schizotaxia is a broader construct than schizophrenia. Our empirical studies suggest that the basic symptoms of schizotaxia occurs in 20% to 50% of first-degree relatives of schizophrenic patients.[40,44] In comparison, only about 10% of relatives will become psychotic, and less than 10% will develop schizotypal personality disorder.[45,46] These figures suggest that schizotaxia does not lead inevitably to schizotypal personality or schizophrenia, but in most cases is a long-term condition. This leads to the question of what type of etiological model accounts best for a long-term biological vulnerability (schizotaxia) that, under some circumstances, leads to more serious conditions (schizophrenia).

Diagnostic criteria for schizophrenia ignore its etiology and pathophysiology

DSM-III (and later versions) explicitly dissociated diagnostic criteria from speculation about etiology to avoid incorporating theories of etiology that were not subjected to empirical tests. At this point, however, DSM-III's rejection of theoretical speculation about etiology should not lead us to reject empirical facts about etiology as being relevant to diagnosis or conceptualization. Moreover, such a view risks a continuing disconnection of treatment from etiology. Since the introduction of antipsychotic medications, pharmacological treatments have focused on alleviating the most acute, florid symptoms of schizophrenia, ie, those related to psychosis. Although several newer antipsychotic medications also alleviate selected negative symptoms and cognitive deficits, treatment remains symptomatic. It is not aimed at correcting specific causes of the disorder, nor is it aimed at preventing its onset.

We recognize how counterintuitive it is to think of psychosis as a somewhat nonspecific end state of schizophrenia. But consider the evidence suggesting that schizophrenia's pathophysiology is put into place long before the first psychotic episode. Many researchers have sketched neurodevelopmental models of schizophrenia based on adverse genetic and environmental interactions occurring as early as the second trimester of life (see, eg, refs 47-55). These events create a neurodevelopmental syndrome, which, as studies of relatives of schizophrenic patients have shown, is characterized by neuropsychological, psychophysiological, and neuroimaging abnormalities.[43] Evidence for neurodevelopmental syndromes in schizophrenia is extensive at this point, and emphasizes clinical, biological, and neuropsychological abnormalities, both in individuals who later develop schizophrenia, and in their nonpsychotic biological relatives. For reasons that are still unknown, this syndrome sometimes leads to psychosis, and sometimes does not. Notably, these indicators of the syndrome are more proximal to schizophrenia's initial causes than is psychosis.

Clinical implications

Schizophrenia as a premorbid condition

Taken together, the evidence described above supports the idea that schizophrenic disease begins before the onset of psychosis, and expresses itself biologically in characteristic ways. One way to integrate these findings is to conceptualize its manifestations (eg, biological abnormalities, biological relatedness to a family mem-

ber with schizophrenia, selected neuropsychological deficits, and history of obstetric complications) as risk factors that vary along dimensions of severity, for schizophrenia. Schizotaxia describes this premorbid, yet clinically significant, neurodevelopmental condition. Psychosis, in contrast, represents a relatively less specific consequence of schizophrenic disease than does schizotaxia. If our view is correct, then the clinical significance of schizotaxia is related to both its (putative) status as a discrete condition, and its status as a risk factor for schizophrenia.

The emphasis on prepsychotic aspects of schizophrenic illness, ie, schizotaxia, has potentially significant implications for the treatment of schizophrenia. For one, the identification of a premorbid condition, especially one that is itself significant clinically, will facilitate the development of early intervention strategies. Cameron (cited in ref 56) first described, in 1938, the need to treat schizophrenia early to prevent subsequent deterioration. As noted earlier, evidence has since accumulated to support the view that the longer treatment is delayed, the poorer the subsequent prognosis.[27,57,58]

Other benefits of early treatment are also likely, such as the delay or prevention of the social, interpersonal, cognitive, and affective disruptions that accompany and follow an initial psychotic episode. One potential consequence of secondary prevention is simply the delay of onset. This may be especially valuable for early-onset cases because these patients would then have more time to mature before having to cope with a serious and chronic illness. Moreover, untreated schizophrenia may become more resistant to treatment, in part because psychosis itself may create or lead to widespread neurobiological abnormalities[28] that make treatment more complicated and difficult.

The case for preventive treatment

Research and theory about the early treatment of psychosis naturally leads to the question: can psychosis be avoided? That is, can schizophrenic illness be treated before psychosis is added to it? Most researchers have approached the issue of primary prevention by focusing on prodromal symptoms as indicators of an impending psychotic disorder, but such symptoms are often nonspecific. McGorry et al[59] showed, for example, that DSM-III-R prodromal symptoms for schizophrenia occurred in 15% to 50% of high-school students. This raises obvious questions about the validity—and wisdom—of intervening on the basis of such symptoms. Are prodromal indicators like social withdrawal or subtle changes in thinking or affect valid enough indicators of early schizophrenia to warrant intervention, which may involve powerful antipsychotic medications and their associated side effects? Is the cost/benefit analysis favorable enough to risk the potential anxiety and stigmatization (for both "patients" and their families) that will likely attend the classification of an individual as at-risk for schizophrenia, probably in the near future? Unfortunately, these questions cannot yet be answered in the affirmative. In part because prodromal symptoms that are specific to schizophrenia (or to other psychotic illness) are still unknown,[60] the application of primary prevention programs appears premature in the absence of clear clinical symptoms.

Among the steps that will make prevention efforts more feasible for nonpsychotic individuals are, first, to identify the population at risk, and second, to develop a rationale for treatment. We propose that the study of schizotaxia will help to achieve this goal. Given this hypothesis, what are the next steps that must be taken to design a strategy aimed at preventing schizophrenia? Clearly, the validity of schizotaxia as a predictor of subsequent schizophrenia must be firmly established.

As Robins and Guze[5] pointed out, it is crucial to establish both the concurrent and predictive validity of putative syndromes. Does the classification of schizotaxia predict neuropsychological, neuroimaging, or psychophysiologic findings that are consistent with what is known about the neurobiology of schizophrenia? As we have reviewed elsewhere, a growing body of literature suggests that the answer is "yes."[43] Abnormalities found among relatives of schizophrenic patients include eye-tracking dysfunction,[61] allusive thinking,[62] neurologic signs,[63] characteristic auditory evoked potentials,[64] neuroimaging-assessed brain abnormalities,[65] and neuropsychological impairment.[66]

More importantly, does schizotaxia predict the subsequent emergence of psychotic symptoms or other forms of psychopathology? Studies of children at risk for schizophrenia show that features of schizotaxia do predict subsequent schizophrenia and related disorders (refs 67-70 and Erlenmeyer-Kimling L, 1997, personal communication). Nevertheless, more work is needed to create measures of schizotaxia that will accurately classify children who do and do not go on to develop schizophrenia.

The schizotaxia treatment protocol

Although schizotaxic features cannot yet be used to select preschizophrenic children for primary prevention protocols, our current knowledge about schizotaxia suggests a method for evaluating medications that may someday be useful for the prevention of schizophrenia. This method, which we call the "schizotaxia treatment protocol" is straightforward: select a sample of schizotaxic first-degree relatives of schizophrenic patients and, using standard randomized clinical trial methodology, determine if a putative preventative treatment modifies the features of schizotaxia in an acute trial. Presumably, any medicine that mitigates the features of schizotaxia will be a reasonable candidate for a primary prevention trial when such trials are possible.

The use of the schizotaxia treatment protocol assumes that the syndrome of schizotaxia observed among first-degree relatives of schizophrenic patients shares etiologic and pathophysiologic pathways with preschizophrenic subjects. If this assumption is true, then any medication that targets these pathways to mitigate schizotaxic features may also work to reduce the likelihood of the onset of psychosis. This assumption is reasonable because: (i) first-degree relatives of schizophrenic patients are at high risk for carrying schizophrenia susceptibility genes,[39] and (ii) the features of schizotaxia observed among these relatives are similar to those seen in children who eventually become schizophrenic.[43]

A major advantage of the schizotaxia treatment protocol is that it can avoid some of the ethical issues raised by primary prevention studies of schizophrenia. Prevention studies will label children and adolescents as potential future schizophrenics. As noted above, this opens up the possibility of stigmatization and psychological harm to the subject and their families. It is also possible that medications chosen for prevention trials may pose greater risks to children and adolescents than adults. That would preclude their use in the absence of a solid rationale for efficacy. But, because schizotaxia can be defined in the adult relatives of schizophrenic patients, using an acute schizotaxia trial for putative preventative medicines will not require studies of children or adolescents.

If successful treatments are developed and tested, and the syndrome of schizotaxia is validated, then treatments at earlier ages may be considered. For example, if an acute schizotaxia treatment trial in adults is successful, one might consider an acute trial for adolescents. If an adolescent trial were to be successful, then we might consider a trial to prevent psychosis (assuming that the target, preschizophrenic population could be accurately defined).

One of the difficulties with implementing the schizotaxia treatment protocol is the lack of a consensual definition of schizotaxia. Although we can make many measurements of schizotaxic features (eg, neuropsychological symptoms, negative symptoms, social functioning), the field has yet to agree on how these measures should be combined to create a schizotaxic category.

Tsuang et al[71] recently described a working definition of schizotaxia based on a set of specific criteria for the purpose of developing a treatment protocol. In this initial approach, we diagnosed schizotaxia in people who met the following criteria:

- They had at least one relative with schizophrenia;
- They had estimated IQs of 70 or higher;
- They had none of the following: lifetime history of psychotic disorders; substance abuse diagnosis within 6 months of diagnosis; head injury with documented loss of consciousness exceeding 5 minutes (or subsequent cognitive deficits); history of neurologic disease or damage; medical condition with significant cognitive sequelae; or a history of electroconvulsive treatment;
- They had at least moderate levels of negative symptoms, defined as 6 items rated 3 or higher on the Scale for the Assessment of Negative Symptoms (SANS[72]);
- They had moderate or greater deficits (defined as approximately two or more standard deviations below appropriate norms) in at least one of three cognitive domains: vigilance/working memory, long-term verbal memory, and executive functions;
- They were at least one standard deviation below normal in a second cognitive domain (see ref 71) for lists of specific tests and measures on tests used to meet the neuropsychological criteria).

Our decision to require moderate deficits in different domains ensured that our initial treatment attempts would include only adults with demonstrable clinical and neuropsychological difficulties. This was important to demonstrate both the clinically meaningful nature of schizotaxia, and also to make the risk/benefit assessment of treatment more favorable.

Our first application of the schizotaxia treatment pro-

tocol[71] used risperidone, a novel antipsychotic medication. As we noted above, trials of these medications would appear reasonable on the basis of our assumption that individuals with schizotaxia share etiological and psychopathological elements with schizophrenia. Trials with the older, typical antipsychotics, however, were limited by reluctance to use these medications in nonpsychotic populations, mainly because of their side effects and subsequently high rates of noncompliance,[73] but also because of their essential inability to alleviate negative symptoms[74] or neuropsychological deficits.[75]

Another reason we chose risperidone was that, compared with other novel antipsychotic medications, it had (at the inception of the study) been shown to reduce positive and some negative symptoms in schizophrenia.[74,76,77] It was clearly safer than typical neuroleptics, in that it produced fewer extrapyramidal side effects (at least at lower doses, eg, refs 74, 77). Notably, it also improved cognitive functions in schizophrenia, especially in attention or working memory,[76,78,79] but possibly in verbal long-term memory[79] and executive functions[76] as well. This latter feature was especially important given that neuropsychological impairment is a hallmark of schizotaxia.

Based on these issues, we began an open trial of risperidone in people who met our criteria for schizotaxia.[71] After all entrance criteria were met, subjects received low doses (starting at 0.25 mg and reaching maximum doses of 2.0 mg) of risperidone for 6 weeks. During that period, they were evaluated weekly for side effects and for clinical and neuropsychological effects of treatment. After 6 weeks, most clinical and neuropsychological tests were repeated. We reported on the effects of treatment in our first 4 cases[71] and have since completed a fifth case. All subjects thus far showed marked improvements in a demanding test of auditory attention, and all subjects showed reduced negative symptoms after 6 weeks. In 3 cases, reductions in negative symptoms were marked; in 2 they were modest. Side effects, when they occurred, were mild to moderate in severity. No one requested the discontinuation of treatment, but in some cases the doses were lowered to reduce discomfort.

Future directions

Our initial application of the schizotaxia treatment protocol is encouraging, as all 5 cases showed reductions in negative symptoms and neuropsychological deficits. We stress the preliminary nature of these findings, however, and do not yet recommend the use of risperidone or other medications to treat schizotaxia. Larger, controlled studies are needed to determine if the treatment implications of these pilot findings are correct.

Despite this caveat, however, our findings suggest the feasibility of developing treatment strategies for adult schizotaxia. It is clear that we are only starting this process. Perhaps the most important tasks for the near future, in addition to the need for more methodologically rigorous replications, is the validation of schizotaxia as a syndrome. In order to accomplish this task, it will be useful to change our conceptualization of schizophrenia somewhat from the historical view of a discrete, categorical entity whose diagnosis depends on the clinical symptoms of psychosis. Instead, a more fruitful approach may be to incorporate a dimensional, neurodevelopmental perspective in schizophrenia that includes neurobiological and neuropsychological measures occurring prior to the development of psychosis (schizotaxia). At some point, molecular biological data will also be included in this conception, as the genes that cause schizotaxia are located. As the validity of schizotaxia becomes established, the risk (for subsequent psychosis) provided by its component features will become measurable. That knowledge base will provide the foundation for strategies aimed at the prevention of schizophrenia, perhaps in the not-too-distant future. ❑

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Conceptualizaciones respecto al riesgo de padecer esquizofrenia: sus implicancias clínicas

Históricamente, los criterios diagnósticos del Diagnostic and Statistical Manual of Mental Disorders *(DSM) para esquizofrenia han enfatizado algunas características que incluyen: síntomas de psicosis, una disociación de síntomas de su etiología, una dependencia de los síntomas clínicos y una aproximación categorial para clasificar el trastorno. Aunque este enfoque resulta bastante útil, también tiene sus limitaciones. En este artículo se revisan estas limitaciones y se señala la importancia de incorporar datos recientes, provenientes de investigaciones acerca de los aspectos genético-biológicos y del neurodesarrollo de la esquizofrenia, en las concepciones actuales de este trastorno. También se revisa el concepto de "esquizotaxia", que engloba este punto de vista; aparece antes del comienzo de la psicosis e hipotéticamente representaría la vulnerabilidad a la esquizofrenia. Si esta hipótesis en este punto es correcta, significa que la identificación de individuos con esquizotaxia eventualmente facilitaría el desarrollo de estrategias de prevención al reconocer una condición premórbida (pero clínicamente significativa) para la esquizofrenia. Sin embargo, la identificación de componentes biológicos o neuropsicológicos de la esquizotaxia facilitaría bases más específicas para el desarrollo de nuevas intervenciones terapéuticas. Nuestros intentos iniciales para desarrollar protocolos para la evaluación y tratamiento de la esquizotaxia son alentadores y se revisan en este artículo.*

Conceptualisation d'une prédisposition à la schizophrénie : implications cliniques

Traditionnellement, les critères diagnostiques du Diagnostic and Statistical Manual of Mental Disorders *(DSM) pour la schizophrénie ont mis l'accent sur différents aspects, notamment les symptômes psychotiques; l'indépendance entre symptômes et étiologie; la place prépondérante de la clinique et une approche catégorielle pour classer ce trouble. Cependant, bien que les caractéristiques ainsi définies aient leur utilité, elles ont aussi des limites. Le présent article passe ces dernières en revue, et souligne l'importance d'intégrer dans les conceptions actuelles de la schizophrénie les données récentes sur les origines génétiques/biologiques et neurodéveloppementales de cette maladie. Cet article fait également le point sur le concept de "schizotaxie", qui survient avant l'apparition de la psychose, et constituerait une prédisposition à la schizophrénie. Si notre hypothèse concernant ce point s'avère exacte, l'identification des personnes schizotaxiques pourrait faciliter le développement de stratégies préventives en déterminant un état prémorbide (mais cliniquement significatif) de la schizophrénie. De plus, l'identification des composantes biologiques et neuropsychologiques de la schizotaxie devrait fournir des bases plus spécifiques pour le développement de nouveaux traitements. Nos premières tentatives de mise en place de protocoles pour l'évaluation et le traitement de la schizotaxie, décrites ici, paraissent d'ores et déjà encourageantes.*

REFERENCES

1. Kraepelin E. *Dementia Praecox and Paraphrenia.* Huntington, NY: Robert Krieger; 1919/1971.
2. Bleuler E. *Dementia Praecox or the Group of Schizophrenias.* New York, NY: International Universities Press; 1911/1950.
3. Cooper J, Kendell R, Gurland B, et al. *Psychiatric Diagnosis in New York and London: A Comparative Study of Mental Hospital Admissions.* London, UK: Oxford University Press; 1972.
4. Klerman GR. Historical background. In: Cavenar JO, ed. *Psychiatry.* Vol 1. Philadelphia, Pa: J.B. Lippincott Company; 1988.
5. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *A J Psychiatry.* 1970;126:983-987.
6. Meehl P. Diagnostic taxa as open concepts: metatheoretical and statistical questions about reliability and construct validity in the grand strategy of nosological revision. In: Millon T, Klerman G, eds. *Contemporary Directions in Psychopathology: Toward the DSM-IV.* New York, NY: Guilford Press; 1986:215-232.
7. Blashfield RK. The Classification of Psychopathology: Neo-Kraepelinian and Quantitative Approaches. New York, NY: Plenum; 1984.
8. Schneider K. *Clinical Psychopathology.* New York, NY: Grune & Stratton; 1959.
9. Peralta V, Cuesta MJ. Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. *Br J Psychiatry.* 1998;174:243-248.
10. Peralta V, Cuesta MJ, Farre C. Factor structure of symptoms in functional psychoses. *Biol Psychiatry.* 1997;42:806-815.
11. Ratakonda S, Gorman JM, Yale SA, Amador XF. Characterization of psychotic symptoms: use of the domains of psychopathology model. *Arch Gen Psychiatry.* 1998;55:75-81.
12. Bell RC, Dudgeon P, McGorry PD, Jackson HJ. The dimensionality of schizophrenia concepts in first-episode psychosis. *Acta Psychiatr Scand.* 1998;97:334-342.
13. Serretti A, Macciardi F, Smeraldi E. Identification of symptomatic patterns common to major psychoses: proposal for a phenotype definition. *Am J Med Genet. (Neuropsychiatr Genet.)* 1996;67:393-400.
14. Crow TJ. From Kraepelin to Kretschmer leavened by Schneider. *Arch Gen Psychiatry.* 1998;55:502-504.
15. Monti MR, Stanhellini G. Psychopathology: an edgeless razor? *Compr Psychiatry.* 1996;37:196-204.
16. Kendler KS, Karkowski LM, Walsh D. The structure of psychosis. *Arch Gen Psychiatry.* 1998;55:492-499.
17. Maziade M, Bissonnette L, Rouillard E, et al. 6p24-22 region and major psychoses in the eastern Quebec population. *Am J Med Genet. (Neuropsychiatr Genet.)* 1997;74:311-318.
18. Wildenauer D, Hallmayer J, Albus M. A susceptibility locus for affective and schizophrenic disorder? *Psychiatr Genet.* 1996;6:152.
19. Wildenauer DB, Schwab SG, Maier W, Detera-Wadleigh SD. Do schizophrenia and affective disorder share susceptibility genes? *Schizophr Res.* 1999;39:107-111.
20. Bertelsen A, Gottesman II. Schizoaffective psychoses: genetical clues to classification. *Am J Med Genet.* 1995;60:7-11.
21. Maier W, Lichtermann D, Minges J, et al. Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Arch Gen Psychiatry.* 1993;50:871-883.
22. Ginns EI, Ott J, Egeland JA, et al. A genome-wide search for chromosomal loci linked to bipolar affective disorder in the old order Amish. *Nat Genet.* 1996;12:431-435.
23. Tsuang MT, Stone WS, Faraone SV. Schizophrenia: a review of genetic studies. *Harv Rev Psychiatry.* In press.
24. Foroud T, Castellucio PF, Koller DL, et al. Genomewide scan of affected relative pairs using the NIMH Genetics Initiative bipolar affective disorder pedigrees. *Am J Med Genet.* 1998;81:462.
25. Rice JP, Goate A, Williams JT, et al. Initial genome scan of the NIMH Genetics Initiative bipolar pedigrees: chromosomes 1, 6, 8, 10, and 12. *Am J Med Genet. (Neuropsychiatr Genet.).* 1997;74:247-253.
26. Faraone SV, Matise T, Svrakic D, et al. A genome scan of the European-American schizophrenia pedigrees of the NIMH Genetics Initiative. *Am J Med Genet. (Neuropsychiatr Genet.).* 1998;81:290-295.
27. Wyatt RJ. Early intervention for schizophrenia: can the course of the illness be altered? *Biol Psychiatry.* 1995;38:1-3.
28. Knoll JL, Garver DL, Ramberg JE, Kingsbury SJ, Croissant D, McDermott B. Heterogeneity of the psychoses: is there a neurodegenerative psychosis? *Schizophr Bull.* 1998;24:365-379.
29. Keverne EB. GABA-ergic neurons and the neurobiology of schizophrenia and other psychoses. *Brain Res Bull.* 1999;48:467-473.
30. Crow TJ. The search for the psychosis gene. *Br J Psychiatry.* 1991;158:611-614.
31. Crow TJ. The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture. *Br J Psychiatry.* 1990;156:788-797.
32. Crow TJ. Nuclear schizophrenic symptoms as a window on the relationship between thought and speech. *Br J Psychiatry.* 1998;173:303-309.
33. Collinge J, DeLisi LE, Boccio A, et al. Evidence for a pseudo-autosomal locus for schizophrenia using the method of affected sibling pairs. *Br J Psychiatry.* 1991;158:624-629.
34. Parfitt E, Asherson P, Sargeant M, Whatley S, McGuffin P, Owen M. A linkage study of the pseudoautosomal region in schizophrenia. *Psychiatr Genet.* 1991;2:92-93. Abstract.
35. DeLisi LE, Devoto M, Lofthouse R, et al. Search for linkage to schizophrenia on the X and Y chromosomes. *Am J Med Genet. (Neuropsychiatr Genet.)* 1994;54:113-121.
36. Frances AJ, First MB, Widiger TA, et al. An A to Z guide to DSM-IV conundrums. *J Abnorm Psychol.* 1991;100:407-412.
37. Gunderson JG, Links PS, Reich JH. Competing models of personality disorders. *J Pers Disord.* 1991;5:60-68.
38. Toomey R, Faraone SV, Simpson JC, Tsuang MT. Negative, positive, and disorganized symptom dimensions in schizophrenia, major depression, and bipolar disorder. *J Nerv Ment Dis.* In press.
39. Gottesman II. *Schizophrenia Genesis: The Origin of Madness.* New York, NY: Freeman; 1991.
40. Faraone SV, Kremen WS, Lyons MJ, Pepple JR, Seidman LJ, Tsuang MT. Diagnostic accuracy and linkage analysis: how useful are schizophrenia spectrum phenotypes? *Am J Psychiatry.* 1995;152:1286-1290.
41. Meehl PE. Schizotaxia, schizotypy, schizophrenia. *Am Psychol.* 1962;17:827-838.
42. Meehl PE. Schizotaxia revisited. *Arch Gen Psychiatry.* 1989;46:935-944.
43. Faraone SV, Green AI, Seidman LJ, Tsuang MT. "Schizotaxia": clinical implications and new directions for research. *Schizophr Bull.* In press.
44. Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Lyons MJ, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. *J Abnorm Psychol.* 1995;104:286-304.
45. Battaglia M, Bernardeschi L, Franchini L, Bellodi L, Smeraldi E. A family study of schizotypal disorder. *Schizophr Bull.* 1995;21:33-45.
46. Battaglia M, Torgersen S. Schizotypal disorder: at the crossroads of genetics and nosology. *Acta Psychiatr Scand.* 1996;94:303-310.
47. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987;44:660-669.
48. Weinberger DR. Schizophrenia as a neurodevelopmental disorder: a review of the concept. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia.* London, UK: Blackwood Press; 1994.
49. Weinberger DR. Neurodevelopmental perspectives on schizophrenia. In: Bloom FE, Kupler DJ, eds *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press; 1995:1171-1183.
50. Seidman LJ. The neuropsychology of schizophrenia: a neurodevelopmental and case study approach. *J Neuropsychiatr Clin Neurosci.* 1990;2:301-312.
51. Goldman-Rakic PS. More clues to "latent" schizophrenia point to developmental origins. *Am J Psychiatry.* 1995;152:1701-1703.
52. Woods BT. Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *Am J Psychiatry.* 1998;155:1661-1670.
53. Cannon TD, Mednick SA, Parnas J, Schulsinger F, Praestholm J, Vestergaard A. Developmental brain abnormalities in the offspring of schizophrenic mothers. II. Structural brain characteristics of schizophrenia and schizotypal personality disorder. *Arch Gen Psychiatry.* 1994;51:955-962.
54. Cannon TD. Abnormalities of brain structure and function in schizophrenia: implications for etiology and pathophysiology. *Ann Med.* 1996;28:533-539.
55. Tsuang MT, Faraone SV. The case for heterogeneity in the etiology of schizophrenia. *Schizophr Res.* 1995;17:161-175.
56. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull.* 1996;22:305-326.

57. Green AI, Schildkraut JJ. Should clozapine be a first-line treatment for schizophrenia? The rationale for a double-blind clinical trial in first-episode patients. *Harv Rev Psychiatry.* 1995;3:1-9.
58. Wyatt RJ, Apud JA, Potkin S. New directions in the prevention and treatment of schizophrenia: a biological perspective. *Psychiatry*. 1996;59:357-370.
59. McGorry PD, McFarlane C, Patton GC. The prevalence of prodromal features of schizophrenia in adolescence: a preliminary survey. *Acta Psychiatr Scand.* 1995;92:241-249.
60. Larsen TK, Opjordsmoen S. Early identification and treatment of schizophrenia: conceptual and ethical considerations. *Psychiatry*. 1996;59:371-380.
61. Levy DL, Holzman PS, Matthysse S, Mendell NR. Eye tracking and schizophrenia: a selective review. *Schizophr Bull.* 1994;20:47-62.
62. Catts SV, McConaghy N, Ward PB, Fox AM, Hadzi-Pavlovic D. Allusive thinking in parents of schizophrenics. Meta-analysis. *J Nerv Ment Dis.*1993;181:298-302.
63. Erlenmeyer-Kimling L, Cornblatt B, Friedman D et al. Neurological, electrophysiological, and attentional deviations in children at risk for schizophrenia. In: Henn FA, Nasrallah HA, eds. *Schizophrenia as a Brain Disease.* New York, NY: Oxford University Press; 1982:61-98.
64. Friedman D, Squires-Wheeler E. Event-related potentials (ERPs) as indicators of risk for schizophrenia. *Schizophr Bull.* 1994;20:63-74.
65. Seidman LJ, Faraone SV, Goldstein JM, et al. Reduced subcortical brain volumes in nonpsychotic siblings of schizophrenic patients: a pilot MRI Study. *Am J Med Genet. (Neuropsychiatr Genet.)* 1997;74:507-514.
66. Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV. Neuropsychological risk indicators for schizophrenia: a review of family studies. *Schizophr Bull.* 1994;20:103-119.
67. Dworkin R, Lewis J, Cornblatt B, Erlenmeyer-Kimling L. Social competence deficits in adolescents at risk for schizophrenia. *J Nerv Ment Dis.* 1994;182:103-108.
68. Ledingham J. Recent developments in high risk research. In: Lahey BB, Kazdin AE, eds. *Advances in Clinical Child Psychology.* New York, NY: Plenum Press; 1990:91-137.
69. Auerbach J, Hans S, Marcus J. Neurobehavioral functioning and social behavior of children at risk for schizophrenia. *Isr J Psychiatry Relat Sci.* 1993;30:40-49.
70. Olin SC, Mednick SA. Risk factors of psychosis: identifying vulnerable populations premorbidly. *Schizophr Bull.* 1996;22:223-240.
71. Tsuang MT, Stone WS, Seidman LJ, et al. Treatment of nonpsychotic relatives of patients with schizophrenia: four case studies. *Biol Psychiatry*. 1999;41:1412-1418.
72. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Iowa: The University of Iowa; 1983.
73. Hymowitz P, Frances A, Jacobsberg LB, Sickles M, Hoyt R. Neuroleptic treatment of schizotypal personality disorders. *Compr Psychiatry.* 1986;27:267-271.
74. Marder S, Meibach R. Risperidone in the treatment of schizophrenia. *Am J Psychiatry.* 1994;151:825-835.
75. Cassens G, Inglis AK, Appelbaum PS, Gutheil TG. Neuroleptics: effects on neuropsychological function in chronic schizophrenic patients. *Schizophr Bull.* 1990;16:477-499.
76. Rossi A, Mancini F, Stratta P, et al. Risperidone, negative symptoms and cognitive deficit in schizophrenia: an open study. *Acta Psychiatr Scand.* 1997;95:40-43.
77. Tamminga CA. The promise of new drugs for schizophrenia treatment. *Can J Psychiatry.* 1997;42:265-273.
78. Green MF, Marshall BDJ, Wirshing WC, et al. Does risperidone improve verbal working memory in treatment-resistant schizophrenia? *Am J Psychiatry.* 1997;154:799-804.
79. Stip E. The effect of risperidone on cognition in patients with schizophrenia. *Can J Psychiatry.* 1996;41:S35-S40.

Psychostimulants in the therapy of treatment-resistant depression

Review of the literature and findings from a retrospective study in 65 depressed patients

Gabriele Stotz, MD, PhD; Brigitte Woggon, MD; Jules Angst, MD

Gabriele STOTZ

The use of psychostimulants in the therapy of treatment-resistant depression in addition to conventional antidepressants is not very common and has been criticized by some authors. In Germany, Austria, and Switzerland, depression is not a listed indication for the use of psychostimulants. In contrast, at the Zurich Psychiatric University Hospital, dextroamphetamine and ritalin have been used since the thirties to treat severe cases of treatment-resistant depression, especially in the presence of prominent fatigue and apathy, and psychostimulants are now well established as an adjuvant therapy. This article reviews the literature on the use of psychostimulants in treatment-resistant depression and discusses the findings relative to therapeutic efficacy, side effects, and frequency of dependency from a retrospective study carried out in 65 patients of our hospital treated with psychostimulants.

The use of psychostimulants as an adjuvant therapy in treatment-resistant depression is not very common nowadays and has been the subject of much criticism. This article gives a brief review of the literature and reports on the findings from a retrospective study carried out in 65 depressed patients treated with psychostimulants (amphetamine and methylphenidate) in addition to conventional antidepressants. Thirty-eight out of 65 patients showed significant improvement, in particular with respect to energy, mood, and psychomotor activity. The best response to psychostimulants was seen in inhibited types of depression and in combination with a tricyclic antidepressant. None of the patients developed drug dependency. The incidence of side effects was low, and agitation and restlessness improved with an additional short-term treatment with benzodiazepines. It is concluded that the rapid onset of action (2-3 hours) after administration may help cover the therapeutic latency period of conventional antidepressants and probably potentiates their effect. In view of their potential benefits in treatment-resistant depressive states, psychostimulants should be tried more often.

Keywords: *psychostimulant; adjuvant therapy; treatment-resistant depression; combination with tricyclics; dependency; rapid onset; potentiation of antidepressant effect*

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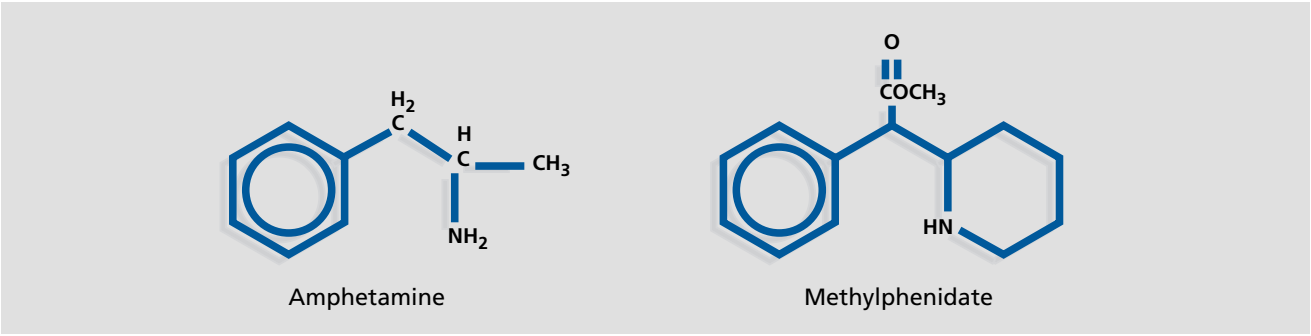

Figure 1. Structure of amphetamine and methylphenidate.

Review of the literature

Historical background

Amphetamine was first synthesized in 1887, with the first significant clinical investigations being performed in 1927.[1] The drug was used as a bronchodilator in asthma, as an appetite suppressant, for narcolepsy, and, paradoxically, was discovered in the 1930s to alleviate the hyperactive syndrome in children.

Since the 1930s, amphetamine and its derivatives methylphenidate and pemoline have been used in affective disorders, obsessive-compulsive disorders, and in schizophrenia (for a review see ref 2) *(Figure 1)*. However, in the 1950s, psychostimulants were replaced by the newly developed antidepressants. Their use was reduced still further in the 1960s, as these drugs were being increasingly abused.[3,4] In recent years, the use of psychostimulants in psychiatry has been limited to the therapy of attention deficit disorder (for a review see ref 5), refractory obesity, and narcolepsy. Most psychiatrists today are not familiar with the potential usefulness of psychostimulants in the therapy of treatment-resistant depression.

Pharmacology

Amphetamine increases the release of biogenic amines, exerts direct agonistic effects on presynaptic central receptors for 5-hydroxytryptamine (5-HT), and has a mild inhibiting effect on monoamine oxidase.[6,7] Thus, from a pharmacological viewpoint, psychostimulants complete and amplify the effect of conventional antidepressants[8-14] and are assumed to increase the blood levels of certain antidepressants through their action on hepatic hydroxylation.[13]

Psychostimulants are rapidly absorbed following oral administration. At standard therapeutic doses (10 to 15 mg for amphetamine and 10 to 60 mg for methylphenidate), peak effects are found 2 to 3 hours after ingestion. Psychostimulants are metabolized by rapid oxidative deamination to benzoic acid and hippuric acid.

Clinical effects

The greatest improvement reported following treatment with psychostimulants is in motor activity, mood, and psychomotor activity.[15-17] An improvement in memory and concentration may be observed, in some cases accompanied by euphoria.[18]

The onset of action of psychostimulants is usually observed clinically within 30 minutes to 1 or 2 hours following administration,[19-23] and their effects last about 4 hours.[24]

Patient response is heterogeneous, with variations in sensitivity due to individual differences in biological and genetic parameters.[25] The use of psychostimulants must be carefully monitored.[10] Patient response also depends on which type of psychostimulant is administered, and if no therapeutic effect is observed with one drug, another one may prove effective. Furthermore, patient response to a given psychostimulant may vary from year to year.[16] One feature of particular interest is that the response to amphetamines may be predictive of the therapeutic effect of tricyclic drugs in depressed patients, since both types of drugs have similar mechanisms of action (rapid for the amphetamines,

slower for the tricyclics) involving an increase in free norepinephrine levels.[19] In contrast, the response to methylphenidate does not appear to be predictive of antidepressant efficacy.[26]

Side effects

At low doses (2-10 mg per day), amphetamine can induce sleep and libido disturbances as well as nausea, tremor, agitation, and restlessness.
At higher doses (30-60 mg per day), amphetamine may induce anxiety, psychoses, exhaustion symptoms with fatigue and drowsiness after the stimulation phase, prolonged depression, and prolonged hallucinosis[27] whereby the individual continues to hallucinate after the drug has been metabolized.[28]
Extein[29] described choreoathetosis after administration of psychostimulants in one patient, probably by potentiation of central dopaminergic activity. Because of the release of norepinephrine and dopamine induced by the psychostimulants, the appearance of stereotypic movements and tics is theoretically possible however, these have only been reported in animal experiments in the literature. Other possible yet rare side effects are hyperthermia and pulmonary hypertension[7,30] and, even more rarely, cardiovascular shock and stroke.[31] Natenshon[24] and Ferguson and Funderburk[32] did not observe any effect on the cardiovascular system in their patients. They found neither advanced age nor cardiac disease to contraindicate the use of psychostimulants.
Wilbur[33] noted declining efficacy of stimulants over time; most other authors, however, reported no evidence of waning of effect in depressed patients treated with 5 to 60 mg methylphenidate for up to 1 year.[24] Tolerance was seen only in relation to effects like hyperthermia, hypertonia, and anorexia, but not psychomotor stimulation.[31,34,35]
It should be stressed that the aforementioned side effects are observed not only in depressed patients, but also in patients treated with psychostimulants for other indications.

Development of dependency or tendency to abuse?

The possible development of dependency and a withdrawal syndrome after withdrawing amphetamines has been a controversial issue. Addiction was reported by Kramer et al[3] and Edison,[36] and a withdrawal syndrome characterized by apathy, decreased activity, and sleep disturbances with an increase in rapid eye movement (REM) sleep by Oswald and Thacore[37] and Watson et al.[38] Most studies, however, report little or no dependence in depressed patients treated with amphetamines (see overview in refs 2 and 23). Psychostimulants may be withdrawn after several weeks of treatment without any danger of recurrence of depression.[21] No tolerance or addiction has been reported to develop in geriatric patients. However, recurrence of mild depression, tiredness, and anxiety have been reported on stopping treatment with psychostimulants.[39] Development of tolerance or abuse after patients are discharged from hospital is practically never reported.[22,24,40]

Dosage

The dosage of the psychostimulants must imperatively be individually adjusted. The daily doses usually recommended in treatment-resistant depressed patients range between 2.5 mg[41] and 15 mg[20] for amphetamine and between 10 and 60 mg for methylphenidate.[42]

Indications in depressive disorders

Some depressive disorders remain refractory to treatment despite intensive antidepressant therapy with adequate dosages and even combinations of antidepressants.[43,44] These cases may benefit from adjuvant treatment with psychostimulants. The mood-elevating effects of the tricyclics, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) usually only manifest after 10 to 12 days. Side effects and drug interactions are quite common with these drugs. Although psychostimulants themselves are not as effective as conventional antidepressants,[45,46] they have the dual advantage of a more rapid onset of action and of inducing a lower rate of adverse events.
Because their acute effects develop within less than a few hours,[20] they may be used in combination with traditional antidepressants in order to cover the latter's therapeutic latency period and potentiate their effect.[13,35]
In a review of the literature, Chiarello and Cole[2] showed that the majority of studies—even though some were methodologically unsatisfactory—reported beneficial effects following administration of psychostimulants in treatment-resistant depression.[15,22,31,34,35,47-52] Nevertheless,

no significant advantage of psychostimulants over placebo could be demonstrated in any of the placebo-controlled studies. Some authors have reported lack of effect or even deterioration following the addition of psychostimulants.[53-56]

Beneficial effects have been described in particular in depression with marked apathy in elderly patients.[32,52,57-60] Administration of psychostimulants appears to enhance the efficacy of concomitant (analytically orientated) psychotherapy in elderly patients by facilitating communication and cooperation through their mood-elevating effects.[31]

Psychostimulants are suggested to be of significant value in the management of depression in the elderly as well as in depressed patients with concomitant somatic disorders,[14,21,22,60] and good results have been reported in the treatment of secondary depressions triggered by preexisting somatic diseases.[4,21,40,61]

Psychostimulants have been shown to be effective in patients with mild depressive symptoms in an outpatient setting.[15,55,62]

According to Rudolf,[49,63] the addition of psychostimulants in patients with treatment-resistant depression receiving conventional antidepressants is superior to electroconvulsive therapy (ECT). Kerenyi et al[15] reported methylphenidate to be useful in combination with ECT. Inhibited patients and depressed patients with bipolar disorder seemed to benefit most from adjuvant treatment with psychostimulants.[15] The response to psychostimulants in patients suffering from neurotic and agitated depression seems to be less satisfactory. Nevertheless, there is no contraindication to psychostimulants in agitated depression.[64]

The combination of psychostimulants with tricyclics and MAOIs has been a very controversial issue. Some authors have criticized the combination of psychostimulants and MAOIs on the basis of the possible development of an adrenergic crisis or the serotonin syndrome. The *Physicians' Desk Reference* even warned against such drug combinations in 1983 because of the possibility of hypertensive crises, which, however, were found to be very rare.[35]

In contrast with the above reports, several series of open clinical trials showed the combination of psychostimulants and MAOIs to be safe (see review in refs 35, 65-67). More recently, authors such as Chiarello and Cole[2] and Little[68] have stressed the frequent effectiveness of the combination of psychostimulants and MAOIs in treatment-resistant depression.

Findings from a retrospective study in 65 depressed patients

Subjects and methods

In a retrospective study, we evaluated all the medical records since the 1950s of patients at the Zurich Psychiatric Hospital who had received psychostimulants because of treatment-resistant depression (defined by Woggon[44] as lack of improvement despite treatment with at least two different antidepressants in adequate dosage for more than 4 weeks). A total of 65 patient records were analyzed (20 males and 45 females). The average age of male patients was 50 years, and that of female patients was 55 years. At the time of treatment, the patients were either hospitalized (inpatients) or undergoing ambulatory treatment as outpatients.

The patients who had received psychostimulants were identified from the hospital pharmacy records, which list the names of all patients having received drugs classified as narcotics. In earlier years, classifications of mental diseases such as the *International Classification of Diseases* (ICD) or *Diagnostic and Statistical Manual of Mental Disorders* (DSM) were not yet available, and diagnoses were descriptive only. Therefore, the classification in this retrospective study had to be done on a syndrome basis. The types of depression for which the patients had been treated with psychostimulants because of their refractory character were (in order of descending frequency): inhibited depression (50), anxious depression (39), agitated depression (21), depression with somatization (21), neurotic depression (20), bipolar disorder (16), and depressive states in schizoaffective disorders (4) with overlapping in symptomatology.

Because of the small number of subjects (65 patients, 17 treated with amphetamines, 35 with methylphenidate, and 13 treated with both amphetamines and methylphenidate), and because a separate statistical analysis of patients treated with amphetamines and those treated with methylphenidate failed to show any significant difference between both groups, it was decided to subsume treatment with amphetamines and with methylphenidate as "treatment with psychostimulants" for the purpose of the study.

The average total duration of psychopharmacological treatment (conventional antidepressants and psychostimulants) was 128 months (10 years, with a median of 84 months (7 years). Seventeen patients were treated with amphetamine, 35 with methylphenidate, and 13 with both amphetamine and methylphenidate, either concomitantly or one after the other.
Regarding conventional antidepressant therapy, prior to receiving psychostimulant treatment, 3 patients had been administered one, 6 patients two, 10 patients three, 6 patients four, and 39 patients five or more antidepressants at various dosages. In 35 of the 65 patients, additional treatment modalities (such as sleep deprivation therapy, light therapy, and ECT) had been used.
Psychostimulants were given in combination with tricyclic antidepressants in 48 cases, with SSRIs in 35 cases, with MAOIs in 8 cases, with lithium in 35 cases, and with carbamazepine in 22 cases. (Some patients received two or more antidepressants and mood stabilizers, in combination with the psychostimulants.)
Dosage was titrated individually and modified during therapy. Patients treated with amphetamines received an average dosage of between 5 and 10 mg per day, the minimum being between 5 and 10 mg, and the maximum 20 mg per day. The average dosage of methylphenidate was 10 to 20 mg per day, with a minimum of 10 mg, and maximum of 40 mg per day. In 25 (out of 64) cases the dosage was increased, in 14 cases it remained unchanged, in 14 cases it was reduced, and in 11 cases it was discontinued. The average duration of psychostimulant therapy was 46 months (approximately 4 years) in the amphetamine group and 57 months (approximately 5 years) in the methylphenidate group. In most cases the treatment was continuous.
Patient characteristics are summarized in *Table I* .

Results

Thirty-eight patients improved on treatment with psychostimulants, whereas 26 remained unchanged or deteriorated.
It must be pointed out that no rating scales or self-rating scores had been used in the patients, since it was not common in the fifties or earlier to evaluate a patient's condition with scales. Patient records therefore only allowed the course of the disease to be qualified as "better," "unchanged," or "worse." In this way it could be shown that there was no significant differences between the different age-groups in terms of outcome (chi-square test and analysis of variance for nonparametric samples).

	Amphetamine	Methylphenidate	Both
Number of patients	17	35	13
Male (n)	3	15	2
Female (n)	14	20	11
Age in years (median)	51	49	51
Age of onset in years (median)	37	37	37
Benzodiazepines (n)	21	36	
Psychostimulant therapy in months (median)	46	5	7
Inhibited/anxious depression (n)	11	25	7
Agitated depression (n)	6	10	6

Table I. Retrospective study; patient characteristics (n=65).

Because there was an overlap in the types of depression, we looked at the distribution of patients in terms of response to psychostimulant treatment with respect to syndrome (agitated depression and inhibited/anxious depression), and with respect to diagnosis (unipolar disorder and bipolar disorder) *(Table II)*. The best response to psychostimulant treatment was seen in the group of inhibited and anxious types of depression (27 out of 42 patients improved). In the group of patients with agitated depression, 11 out of 22 patients were improved. Finally, 8 out of 16 patients with bipolar depression were improved.

Looking now at improvement in the course of depression according to the type of treatment the psychostimulant drug was added on to, improvement was noted in 6 out of 8 patients who were treated with a psychostimulant and an MAOI, in 30 out of 48 patients treated with a psychostimulant and a tricyclic, in 21 out of 35 patients treated with a psychostimulant and an SSRI, in 21 out of 35 patients treated with a psychostimulant and lithium, and in 12 out of 22 patients treated with a psychostimulant and carbamazepine.

Additional treatment with benzodiazepines was required in 21 out of 30 patients treated with amphetamines and in 36 out of 48 patients treated with methylphenidate (13 patients received both drugs).

Overall, the frequency of adverse events and side effects was higher in patients treated with methylphenidate than in patients treated with amphetamines. However, methylphenidate was prescribed in most cases to outpatients and at a relatively higher dosage. Side effects were reported in 51 out of 65 patients treated with psychostimulants, including nausea and headache in 32 patients, restlessness in 29 patients, agitation in 25 patients, sleep disturbances in 18 patients, and circulatory disorders in 6 patients. In all cases blood pressure remained unchanged before, during, and after treatment with psychostimulants.

It has to be taken into consideration, however, that it was not always possible to differentiate between the side effects attributable to the psychostimulants and those attributable to the antidepressants.

None of the depressed patients developed drug dependency or addictive behavior. To test for this possibility, psychostimulant treatment was withdrawn, in most patients, at least once during the course of treatment for a period of 2 days, during which the patients experienced apathy and tiredness, but without developing any craving for psychostimulant or signs of withdrawal.

In the 38 patients who experienced a beneficial effect from treatment with psychostimulants, 35 patients reported an improvement in energy, 26 in mood, 26 in motor activity, 15 in symptoms of psychomotor retardation, 11 in vigilance, and 7 in social interactions. Negative symptoms did not improve in the 4 patients with schizoaffective disorders.

Discussion

Our study highlights the benefit of the administration of psychostimulants in addition to conventional antidepressants in patients with treatment-resistant depression. These findings are concordant with those of the majority of open studies (see the review of the literature in the first part of this paper). There were no severe side effects and only a low incidence of mild and moderate side effects in the patient population we studied, in agreement with the findings described in the litera-

	Better	Unchanged/Worse	Total
Syndrome			
Agitated	11	11	22
Inhibited/anxious	27	15	42
Diagnosis			
Unipolar	30	18	48
Bipolar	8	8	16

Table II. Effects during treatment with psychostimulants (n=65).

ture. Unlike Kramer et al[3] and Edison,[36] we found no evidence of drug dependency in our patients.
Some of our patients were suffering from concomitant somatic illnesses. These patients probably benefited from the treatment with psychostimulants, as reported by Woods et al[22] in their sample of patients with depressive disorders secondary to somatic illnesses.
There were no severe cardiovascular disturbances in our patients.
In several studies in the literature, psychostimulants were used preferentially in elderly persons. In our study, both elderly and younger patients were treated with psychostimulants, with the same positive effect.
No psychoses (as opposed to Lucas and Weiss[27]) were observed in any of our patients treated with psychostimulants.
Some of the patients of our study (6 out of 8) responded positively to combined treatment with (reversible) MAO-A inhibitors (like moclobemide) and psychostimulants, even though this particular combination is regarded as controversial. The positive effect of a combination of psychostimulants with tricyclic antidepressants (as recommended by Spencer[69] and Woggon[70]) was confirmed in our study (30 of 48 patients treated with tricyclics and psychostimulants showed improvement). In agreement with Wharton et al[13] and Feighner et al,[35] we believe that combining a psychostimulant and a tricyclic antidepressant potentiates the action of the latter through an increase in the serum levels of its active metabolites. According to another hypothesis, the beneficial effect could be secondary to an increase in monoamine concentrations in the synaptic cleft.
In our experience, use of psychostimulants in agitated depression may be of benefit, although more rarely so than in inhibited depression, thus confirming the findings of Kerenyi.[15] We also agree with Ward and Lampe[64] that there is no contraindication to the use of psychostimulants in agitated depressed states. Like Wilbur,[33] but in disagreement with Wheatley,[50] we have also used psychostimulants in neurotic depression, again with lower rates of success. Finally, we have found that treatment with psychostimulants in an outpatient clinical setting was possible without any problems in some of our patients, a finding in keeping with previous studies of Kerenyi,[15] Rickels et al,[62] and Mattes.[55]

Conclusions

Based on a retrospective study carried out in 65 patients suffering from treatment-resistant depression, we confirm that treatment with psychostimulants in addition to conventional antidepressants has a beneficial effect on the outcome of depression. Not all the patients in our study showed a significant improvement, but the majority (38 out of 65 patients) did. None of the patients developed drug dependency or withdrawal symptoms. The overall incidence and severity of side effects was low. In patients in whom agitation or restlessness developed, a dosage-reduction and/or additional short-term treatment with benzodiazepines proved consistently helpful. Apathy improved in a satisfactory way in most of the patients and in most cases within the first hours following administration. The rapid onset of action of the psychostimulants has the advantage of covering the therapeutic latency period of conventional antidepressants and potentiating their effect. Psychostimulants should be preferably combined with tricyclic antidepressants. In some cases, an increase in dosage of conventional antidepressants can be avoided by taking advantage of the potentiating and additive effect of the psychostimulants.
Although adjuvant therapy with psychostimulants in patients suffering from treatment-resistant depression has not yet become established in clinical practice, we believe that it should be tried more often in view of its potential benefits. ❑

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Fármacos psicoestimulantes en el tratamiento de la depresión resistente

Análisis de la literatura y resultados de un estudio retrospectivo en 65 pacientes con depresión

El uso de psicoestimulantes como fármacos potenciadores en el tratamiento de las depresiones resistentes no es muy frecuente en la actualidad y sigue siendo motivo de críticas. Este artículo revisa parte de la lieratura y refiere los resultados de un estudio retrospectivo realizado en 65 pacientes con depresión que recibieron psicoestimulantes (anfetamina y metilfenidato) además de antidepresivos convencionales. Treinta y ocho pacientes mostraron una mejoría significativa de la energía, el ánimo y la actividad psicomotora. La mejor respuesta a los psicoestimulantes se observó en los pacientes con depresión inhibida que recibieron tricíclicos. Ninguno de los pacientes desarrolló una farmacodependencia. La incidencia de efectos adversos fue baja; la agitación e inquietud se redujeron con benzodiazepinas utilizadas por poco tiempo. Se concluyó que el rápido inicio de la acción de los psicoestimulantes (2 a 3 horas) luego de su administración, puede ayudar a cubrir el período de latencia terapéutica de los antidepresivos convencionales y probablemente potencie el efecto de estos últimos. Los psicoestimulantes debieran utilizarse con más frecuencia en el tratamiento de la depresión resistente considerando sus potenciales ventajas.

Les psychostimulants dans le traitement des dépressions résistantes

Revue de la littérature et résultats obtenus à partir d'une étude rétrospective chez 65 patients déprimés

L'utilisation des psychostimulants comme traitement adjuvant des dépressions résistantes n'est pas très fréquente de nos jours et a été largement critiquée. Cet article donne un aperçu rapide de la littérature et rapporte les résultats d'une étude rétrospective menée chez 65 patients dépressifs cotraités par psychostimulants (amphétamine et méthylphénidate) et antidépresseurs classiques. Trente-huit patients sur 65 ont montré une amélioration significative, en particulier, en ce qui concerne l'énergie, l'humeur et l'activité psychomotrice. La meilleure réponse aux psychostimulants a été notée pour les dépressions ralenties et en association avec un antidépresseur tricyclique. Aucun des patients n'a développé de phénomène de dépendance. La fréquence des effets secondaires était faible, et l'agitation et la nervosité ont été améliorées par une prescription de courte durée de benzodiazépines. En conclusion, la survenue rapide (2 à 3 heures) de l'effet après la prise pourrait aider à couvrir la période de latence thérapeutique des antidépresseurs classiques et, probablement, potentialiser leurs effets. Vu leurs bénéfices potentiels dans le traitement des dépressions résistantes, les psychotimulants devraient être plus fréquemment utilisés.

REFERENCES

1. Leake CD. *The Amphetamines, Their Actions and Uses.* Springfield, Ill: Thomas, CC; 1958.
2. Chiarello RJ, Cole JO. The use of psychostimulants in general psychiatry. A reconsideration. *Arch Gen Psychiatry.* 1987;44:286-295.
3. Kramer JC, Fischman VS, Littlefield DC. Amphetamine abuse. *JAMA*. 1967;201:305-309.
4. Ayd FJ. Psychostimulant therapy for depressed medically ill patients. *Psychiatr Ann.* 1985;15:462-465.
5. Trott GE. *Das Hyperkinetische Syndrom des Kindes- und Jugendalters. Therapeutische Möglichkeiten und deren Evaluation* [Hyperkinetic Syndrome in Children and Youths. Therapeutic Possibilities and Their Evaluation]. (Thesis). Würzburg, Germany; 1991.
6. Goodman LS, Gilman AG. *The Pharmacological Basis of Therapeutics.* 8th ed. New York, NY: McGraw-Hill Companies, Inc; 1990.
7. Forth H, Henschler D, Rummel W. *Allgemeine und Spezielle Pharmakologie und Toxikologie.* 4th ed. Mannheim, Germany: Bibliographisches Institut–Wissenschaftsverlag; 1983.
8. Sulser F, Owens ML, Dingell JV. On the mechanism of amphetamine potentiation by desipramine. *Life Sci.* 1966;5:2005-2010.
9. Dingell JV, Owens ML, Norvich MR, Sulser F. On the role of norepinephrine biosynthesis in the central action of amphetamine. *Life Sci.* 1967;6:1155-1162.
10. Ban TA. The use of the amphetamines in adult psychiatry. *Semin Psychiatry.*1969;1:129-143.
11. Perel JM, Black N, Wharton RN, Malitz S. Inhibition of imipramine metabolism by methylphenidate. *Fed Proc.* 1969;28:418.
12. van Praag HM, Schut T, Bosma E, van den Bergh RA. A comparative study of the therapeutic effects of some 4-chlorinated amphetamine derivatives in depressive patients *Psychopharmacologia*. 1971;20:66-76.
13. Wharton RN, Perel JM, Dayton PG, Malitz S. A potential clinical use for methylphenidate with tricyclic antidepressants. *Am J Psychiatry.* 1971;127:1619-1625.
14. Naor S, Talmon Y. Combined tricyclic antidepressants and Ritalin in elderly depressives [in Hebrew]. *Harefuah*. 1992:123:251-252, 307.
15. Kerenyi AB, Koranyi EK, Sarwer-Foner GJ. Depressive states and drugs. III. Use of methylphenidate (Ritalin) in open psychiatric settings and in office practice. *Can Med Assoc J.* 1960;83:1249-1254.
16. Cameron JS, Specht PG, Wendt GR. Effects of amphetamines on moods, emotions and motivations. *J Psychol.* 1965; 61:93-121.
17. Murray JB. Psychophysiological effects of methylphenidate (Ritalin). *Psychol Rep.* 1987;61:315-336.
18. Smith RC, Davis JM. Comparative effects of d-amphetamine, l-amphetamine and methylphenidate on mood in man. *Psychopharmacology*. 1977;53:1-12.
19. Fawcett J, Siomopoulos V. Dextroamphetamine response as a possible predictor of improvement with tricyclic therapy in depression. *Arch Gen Psychiatry.* 1971;25:247-255.
20. Kiloh LG, Neilson M, Andrews G. Response of depressed patients to methylamphetamine. *Br J Psychiatry.* 1974;125:496-499
21. Fisch RZ. Methylphenidate for medical in-patients *Int J Psychiatry Med.* 1985-1986;15:75-79.
22. Woods SW, Tesar GE, Murray GB, Cassem NH. Psychostimulant treatment of depressive disorders secondary to medical illness. *J Clin Psychiatry.* 1986;47:12-15.
23. Satel SL, Nelson C. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry.* 1989;50:241-249.
24. Natenshon AL. Clinical evaluation of Ritalin. *Dis Nerv Syst.* 1956;17:392-396.
25. Silberman EK, Reus VI, Jimerson DC, Lynott AM, Post RM. Heterogeneity of amphetamine. *Am J Psychiatry.* 1981;138:1302-1307.
26. Little KY. Amphetamine, but not methylphenidate, predicts antidepressant efficacy. *J Clin Psychopharmacol.* 1988;8:177-183.
27. Lucas AR, Weiss M. Methylphenidate hallucinosis. *JAMA*. 1971;217:1079-1081.
28. Smith DE, Fisher CM. An analysis of 310 cases of acute high-dose metamphetamine toxicity in Haight-Ashbury. *Clin Toxicol.* 1970;3:117-124.
29. Extein I. Methylphenidate-induced choreoathetosis. *Am J Psychiatry.* 1978; 135:252-253.
30. Wilson JD, Braunwald E, Isselbacher KJ, et al. Harrisons' Principles of Internal Medicine, 12th ed. New York, NY: McGraw-Hill Companies, Inc; 1991.
31. Jacobson A. The use of Ritalin in psychotherapy of depressions of the aged. *Psychiatr Q.* 1958; 32:474-483.
32. Ferguson JT, Funderburk WH. Improving senile behavior with reserpine and Ritalin *JAMA*. 1956;160:259.
33. Wilbur DL, McLean AR, Allen EV. Clinical observations on the effect of benzedrine sulfate. *JAMA*. 1937;109:549-554.
34. Elizur A, Wintner I, Davidson S. The clinical and psychological effects of pemoline in depressed patients. *Int Pharmacopsychiatry.* 1979;14:127-134.
35. Feighner JP, Herbstein J, Damlouji N. Combined MAOI, TCA and direct stimulant therapy of treatment-resistant depression *J Clin Psychiatry.* 1985;46:206-209.
36. Edison GR. Amphetamines: a dangerous illusion. *Ann Int Med.* 1971; 74:605-610.
37. Oswald J, Thacore VR. Amphetamine and phenmetrazine addiction: physiological abnormalities in the abstinence syndrome. *BMJ*. 1963;issue 5354:427-431.
38. Watson R, Hartmann E, Schildkraut JJ. Amphetamine withdrawal: affective state, sleep patterns and MHPG secretion. *Am J Psychiatry.* 1972;129:263-269.
39. Bare WW, Lin DVP. Stimulants for the aged. Long-term observations with methylphenidate-vitamine-homone combination. *J Am Geriatr Soc.* 1962;10:539-544.
40. Fernandez F, Adams F, Holmes VF, Levy JK, Neidhart M. Methylphenidate for depressive disorders in cancer patients. *Psychosomatics*. 1987;28:455-461.
41. Rudolf GdM. Amphetamine. *Lancet*. 1965;2:131.
42. Gerner RH. Systematic treatment approach to depression and treatment resistant depression *Psychiatr Ann.* 1983;13:37-49.
43. Woggon B. Somatische Therapien: Psychopharmakotherapie [Somatic Therapies: Psychopharmacotherapy]. In: Kisker KP, Lauter H, Meyer JE, Müller C, Strömgren E, eds. Psychiatrie der Gegenwart 5: *Affektive Psychosen.* 1987:289.
44. Woggon B. Psychopharmakologische Behandlung therapieresistenter Depressionen [Psychopharmacological management of treatment-resistant depressions]. *Fundam Psychiatrica.* 1992;6:210-215.
45. Overall JE, Hollister LE, Pokorny AD, Casey JF, Katz G. Drug therapy in depressions. *Clin Pharmacol Ther.* 1961;3:16-22.
46. Hare EH, Dominiak J, Sharpe L. Phenelzine and dexamphetamine in depressive illness. *A comparative trial.* BMJ. 1962;1:9-12.
47. Myerson A, Boston MD. Effect of benzedrine sulfate on mood and fatigue in normal and in neurotic persons. *Arch Neurol Psychiatry.* 1936;36;816-822.
48. Dub LA, Lurie LA. Use of benzedrine in the depressed phase of the psychotic state. *Ohio State Med J.* 1939; 35:39-45.
49. Rudolf GdM. The treatment of depression with desoxyephedrine (Methedrine). *J Ment Sci.* 1949;95:920-929.
50. Wheatley D. Amphetamines in general practice: their use in depression and anxiety *Semin Psychiatry.* 1969;1:163-173.
51. Cookson J, Silverstone T. The effects of methylamphetamine on mood and appetite in depressed patients. *Int Clin Psychopharmacol.* 1986;1:127-133.
52. Warneke L. Psychostimulants in psychiatry. *Can J Psychiatry.* 1990;35:3-10.
53. Robin AA, Wiseberg S. A controlled trial of methylphenidate (Ritalin) in the treatment of depressive states. *J Neurol Neurosurg Psychiatry.* 1958;21:55-57.
54. Hare EH, McCance C, McCormick WO. Imipramine and Drinamyl in depressive illness. *BMJ*. 1964;1:818-820.
55. Mattes JA. Methylphenidate in mild depression: a double-blind controlled trial. *J Clin Psychiatry.* 1985;46:525-527.
56. Darvill FT, Woolley S. Double-blind evaluation of methylphenidate (Ritalin) hydrochloride. *JAMA*. 1959; 169:1739.
57. Ferguson JT. Treatment of reserpine-induced depression with a new analeptic: phenilydate. *Ann NY Acad Sci.* 1955;61:101.
58. Dube AH, Osgood CK, Notkin H. The effects of an analeptic (Ritalin), an ataraxic (reserpine) and a placebo in senile states. *J Chron Dis.* 1957; 5:220-234.
59. Kaplitz SE. Withdrawn, apathetic geriatric patients responsive to methylphenidate. *J Am Geriatr Soc.* 1975;23:271-276.
60. Katon W, Raskind M. Treatment of depression in the medically ill elderly with methylphenidate *Am J Psychiatry*. 1980;137:963-965.
61. Kaufmann MW, Murray GB, Cassem NH. Use of psychostimulants in medically ill patients. *Psychosomatics*. 1982;23:817-819.
62. Rickels K, Gingrich RL, McLaughlin FW, et al. Methylphenidate in mildly depressed outpatients. *Clin Pharmacol Ther.* 1972;13:595-601.

63. Rudolf GdM. The treatment of depression with methylamphetamine. *J Ment Sci.* 1956;4:358-363.
64. Ward NG, Lampe TH. A trial of dextroamphetamine in patients with involutional agitated depression. *J Clin Psychiatry.* 1982;43:35-36.
65. Schuckit M, Robins E, Feighner J. Tricyclic antidepressants and monoamine oxidase inhibitors. *Arch Gen Psychiatry.* 1971;24:509-514.
66. Robie TR, Flora A. Antidepressant chemotherapy, 1965. Rapid response to serotonin precursor potentiated by Ritalin. *Psychosomatics*. 1965;6:351-354.
67. White K, Simpson G. Combined MAOI-tricyclic antidepressant treatment. *J Clin Psychopharmacol.* 1981;1:264-282.
68. Little KY. d-Amphetamine versus methylphenidate: effects in depressed inpatients. *J Clin Psychiatry.* 1993;54:349-355.
69. Spencer S. Depression in general practice managment. *BMJ*. 1965;2:1052-1053.
70. Woggon B. Gibt es Antidepressiva, die bei bestimmten Depressionen speziell indiziert sind? [Are there any antidepressant agents that are specially indicated in specific types of depression?] *Schweiz Med Wochenschr.* 1993;123:1312-1319.

The therapeutic transnosological use of psychotropic drugs

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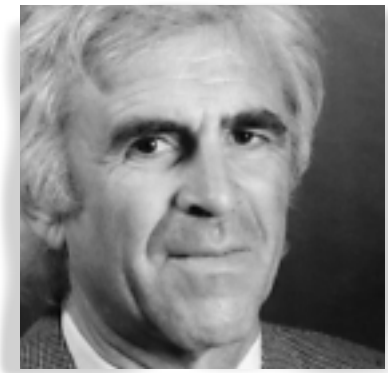

Manfred ACKENHEIL

*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*

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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.

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

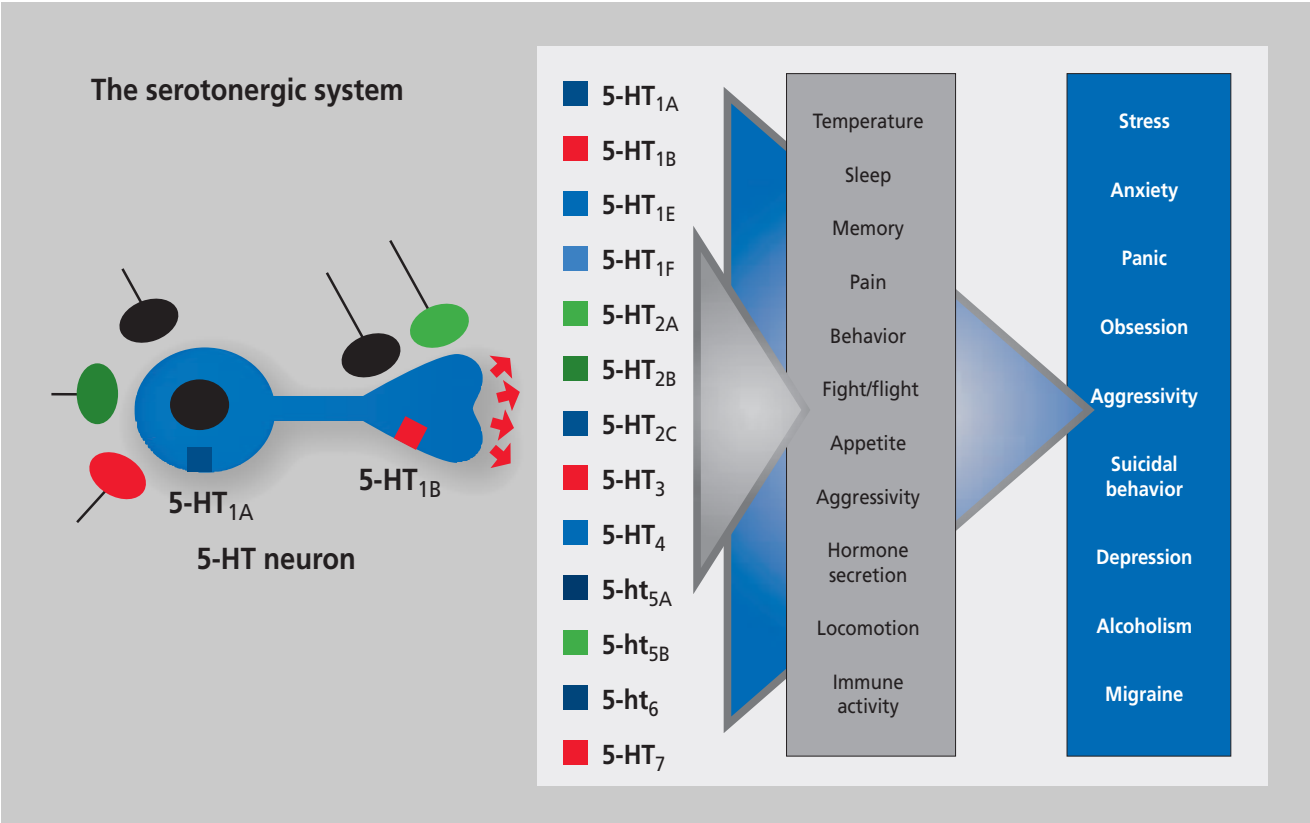


Figure 1. Serotonergic receptors, behaviors, and psychiatric disturbances. After G. Fillion, with permission (ubpublished data).

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

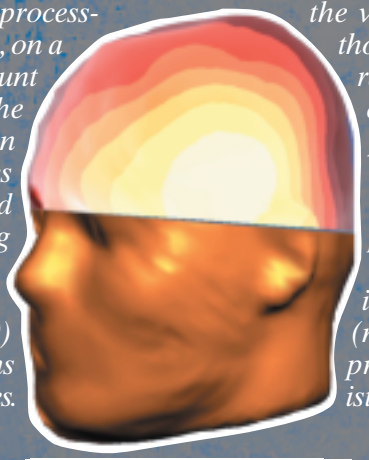
L'utilisation actuelle des psychotropes en pratique clinique est essentiellement transnosologique. Cette attitude est favorisée par la classification en vigueur des maladies mentales (Classification Internationale des Maladies, 10e édition [ICD-10]), et se justifie sans doute si l'on considère que la 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.

Magnetoencephalography of cognitive responses
A sensitive method for the detection of age-related changes

Magnetoencephalography (MEG) is a novel, state-of-the-art technique used in clinical neurophysiology, which promises better understanding of brain (dys)function. The "whole-head" MEG sensor-array enables a noninvasive visualization of the intracellular currents involved in transmission and processing of information in the working brain, on a millisecond timescale, taking into account all (superficial and deep) parts of the CNS simultaneously. 3D reconstruction algorithms are used to attribute sources to anatomically defined structures and cortical subdivisions. MEG recording during the performance of a simple decision-making task using a continuous Go-NoGo paradigm (=P300) enables the evaluation of the mechanisms of attentional and intellectual capabilities. Many psychiatric disorders are related to a state of confusion or disturbances of thought. This poster presents a brief report on fundamental and clinical research into cognitive decline during (normal) aging, carried out with our innovative MEG equipment.

In healthy subjects asked to discriminate high-pitched target tones among standard tones during an oddball detection task, when attention is correctly directed, a particular transient electrical potential is observed, called P300,[1] with maximal amplitudes around the vertex. The underlying generators are thought to be located in the medial temporal lobe regions. We recently demonstrated that MEG signals yield a more complete image of the complex neuronal interactions involved in this type of cognitive response, showing a large positive pole over the left precentral and frontal brain regions (Figure 1) *and a mirror-image pattern in the right hemisphere (not shown).[2] We are currently in the process of localizing the sources in a realistic head model.*



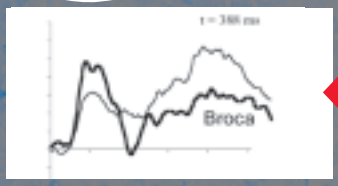


Figure 1. Top: 3D mapping of positive pole of MEG response to target tones. Bottom: averaged tracings in Broca's area for 2 age groups (young [<25 y] —; mid-age [34-47 y], ▬). Note the sustained positive wave >300 ms (horizontal scale 100 ms/division).

Intermezzo 1

In the aging brain, a general attenuation of the P300 response with a slowing of the time to reach the peak in drug-free volunteers (*Figures 1 and 2C, D*) is reported.[3] In young healthy volunteers, this response, characterized by its peak amplitude and peak latency, is known to be at least partly under cholinergic control[4,5] and can be enhanced by psychotropic drugs.[6] In the elderly, nootropic drugs are able to achieve a significant, restoration of P300.[7,8] The proven relationship between psychopharmacology, conscious attention, evoked (cognitive) responses and brain anatomy is a cornerstone concept in biological psychiatry research.

Researchers at our Institute are running programs to explore pathophysiological changes in schizophrenics, abstinent alcoholics, and Alzheimer patients, in comparison with normal aging in control subjects. This is achieved by plotting amplitude and latency parameters for individual subjects as a function of age (Figure 2). *Significant decline is found in subjects at the far ends of our age-range. Regression analysis shows a loss of signal of about 15% with a slowing of 10 to up to 20 ms with every decade of life. Preliminary findings indicate that MEG recordings are able to evidence age-related changes, as do electrical responses, and that these are already clearly visible before the age of 50 years. The slope of change in signal peak parameters is steeper than described in the literature for an even wider range of ages and pathophysiological situations.[9]*

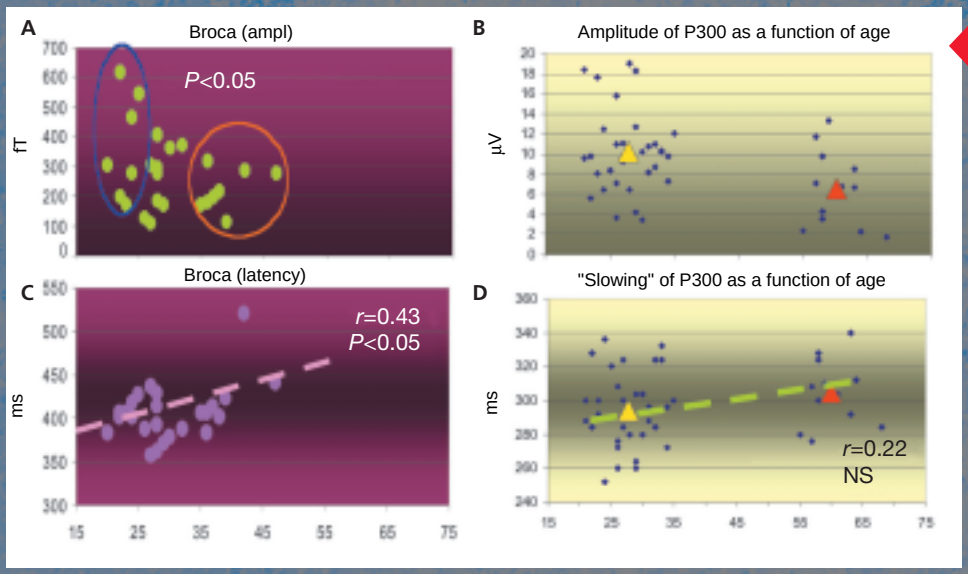


Figure 2. A. Scattergram of amplitude (ampl) for target-specific MEG response in Broca's area; **B.** Mean amplitude of electrical response (P300, Cz electrode) in young (▲) and aged (▲) healthy subjects; **C.** Scattergram of MEG response latency; **D.** mean latency for P300.

In conclusion:
MEG imaging provides a novel means of studying the neuronal events involved in the recruitment of attentional resources, and could herald new discoveries in the field of integrative brain functions.

Intermezzo 2

One of the advantages of MEG as applied to sensory physiology is that straightforward activation maps (eg, auditory response, *see Figure 3*) can be recorded. Source localization through MEG has yielded revolutionary results for the evaluation of impaired hearing, stroke, or epilepsy,[11] and is even able to demonstrate disturbed patterns in schizophrenic patients.[12]

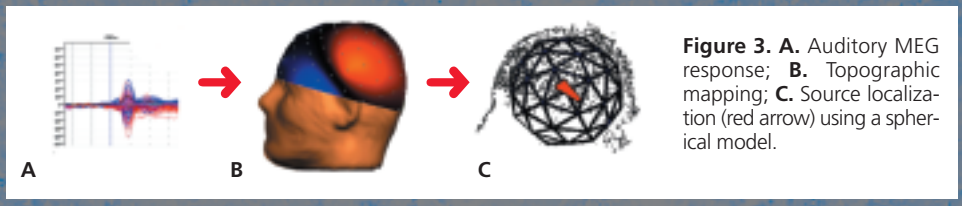


Figure 3. A. Auditory MEG response; **B.** Topographic mapping; **C.** Source localization (red arrow) using a spherical model.

Perspectives: *The sensitivity of MEG in identifying modifications in normal adults makes it a promising diagnostic tool in the early identification of various forms of dementia.[10] Studies are currently being carried out in patients with dementia and related mood disorders, in collaboration with the World Health Organization (WHO), in order to validate the technique.*

REFERENCES
1. Pfefferbaum A, Roth WT, Ford JM. Event-related potentials in the study of psychiatric disorders. *Arch Gen Psychiatry.* 1995;52:559-563. **2.** Boeijinga PH, Soufflet L, d'Ardhuy XL, Toussaint M, Macher JP. P300 and M300; response changes with probability of infrequent stimuli. *Brain Topogr.* 1998;11:75-76. **3.** Polich J. EEG and ERP assessment of normal aging. *Electroencephalogr Clin Neurophysiol.*.1997;104:244-256. **4.** Liogier X, Boeijinga PH, Renault B, et al. Effects of serotonin-selective and classical antidepressants on the auditory P300 cognitive potential. *Neuropsychobiol*. 1999;40:207-213. **5.** Perry E, Walker M, Grace J, Perry R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci.* 1999;22:273-280. **6.** Dierks T, Frölich L, Ihl R, Maurer K. Event-related potentials and psychopharmacology. Cholinergic modulation of P300. *Pharmacopsychiatry*. 1994;27:72-74. **7.** Saletu B, Semlitsch HV, Anderer P, Resch F, Presslich O, Schuster P. The investigation of antihypoxidotic/nootropic drugs (tenilsetam and codergocrine-mesylate) in elderlies with the Viennese Psychophysiological Test System (VPTS). *Methods Find Expt Clin Pharmacol.* 1989;11:43-55. **8.** Semlitsch HV, Anderer P, Saletu B, Binder GA, Decker KA. Cognitive psychophysiology in nootropic drug research: effects of *Ginkgo biloba* on event-related potentials (P300) in age-associated memory impairment. *Pharmacopsychiatry*. 1995;28:134-142. **9.** Polich J. P300 clinical utility and control of variability. *J Clin Neurophysiol.* 1998;15:14-33. **10.** Kugler CF, Taghavy A, Platt D. The event-related P300 potential analysis of cognitive human brain aging: a review. *Gerontology*. 1993;39:280-303. **11.** Stefan H, Schüler P, Abraham-Fuchs P, et al. Magnetic source localization and morphological changes in temporal lobe epilepsy: comparison of MEG/EEG, EcoG and volumetric MRI in presurgical evaluation of operated patients. *Acta Neurol Scand Suppl.* 1994;152:133-134. **12.** Reite M, Teale P, Sheeder J, Rojas D, Simon J. Neuropsychiatric applications of MEG. In: Hashimoto I, Okada YC, Ogawa S, eds. *Visualization of Information Processing in the Human Brain: Recent Advances in MEG and Functional MRI.* EEG suppl 47. 1996

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Validity of nosological classification

Petr Smolik, MD, PhD

The term "nosological classification" is often used in connection with medical classification systems, and the tendency is to equate it with "diagnosis" and "validity." However, particularly in the case of psychiatry, this is far from always being the case. From a scientific point of view, the two most up-to-date classification systems in use today—the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition *(DSM-IV), and the* International Classification of Diseases, 10th Revision *(ICD-10)—may be considered as the theoretical basis of current psychiatric nosology. In this paper we show that the instrumentally generated DSM-IV or ICD-10 diagnoses of schizophrenia have relatively low validity in comparison with clinician expert diagnoses. If medical classification is to be realistic, simple to use, and reliable, nosological systems must be based not only on established facts, but also on theoretical assumptions regarding the nature of disease.*

Keywords: *validity; nosology; DSM-IV; ICD-10; schizophrenia; psychopathology*

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Since their official introduction, the *International Classification of Diseases*, 10th Revision (ICD-10),[1] and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV),[2] operational classification systems have largely become an integral part of the body of knowledge of psychiatrists throughout the world and instruments they constantly refer to. In this article I look at some of the questions that have been raised in connection with these classifications, both as a result of the growing number of critical analyses and of my own experience. This short contribution does not claim to provide exhaustive answers, but merely to stimulate further discussion.

Psychiatrists probably all started adopting operational diagnostic classification systems, such as the ICD and DSM classifications, on the assumption that the reliability of the diagnoses therein defined was unequivocally demonstrated to be very high across the centers and even countries of evaluation, without realizing that the general consensus was based on the lowest level of validity conceivable, since it resulted from the mutual agreement of experts rather than on any proven facts concerning the etiology of mental disorders. This means that in the absence of biological markers for most psychopathological disorders, diagnostic features were based on clinical descriptions, resulting in "official" nosological groupings. One of the main objections raised by clinical psychiatrists was that in many instances diagnoses were based on the numbers of certain symptoms.[3] Nevertheless, in spite of initial warnings of oversimplification, the two most widely used official classifications—DSM and ICD—came to be largely regarded as nosologically valid by medical doctors, official institutions, and even the public at large. The interesting, but logical, paradox is that those least satisfied with these so universally acclaimed classifications are probably the psychiatrists. In this article, I would like to briefly discuss two frequently asked questions: (i) what is the validity of the current diagnostic process? and (ii) what are the weak points of the DSM and ICD classifications?

What is the validity of the current diagnostic process?

Clinical psychiatric practice is mainly based on unstructured interviews. This approach yields excellent results in terms of diagnosis, provided it is carried out by experienced clinicians; unfortunately it is the least objective, reproducible, and reliable one.[4]

The answer to this problem would appear to be validated rating scales, administered by trained examiners. However, although such scales prove very reliable in terms of interrater and intertest results and validity, this applies only to symptoms and syndromes and not to diagnoses.

Structured interviews have relatively high reliability yet lower validity because this type of interview does not provide a framework that makes it possible to follow all the leads that a patient may offer. Previous psychiatric history, information from the entourage, previous response to medication, as well as difficult-to-define features related to "clinical impression" are usually omitted from operational definitions. There is nearly no room for clinical hunches or intuition on the part of the doctor using the DSM-IV or ICD-10 classifications.

Karl Popper is noted for stating that the ultimate test for the validity of a theory is to try to disprove it. If the theory stands the test, we may keep it, but if it fails, then it should be replaced by another theory.[5] With this in mind, I would like to discuss the findings of a study I carried out at the Mental Health Clinical Research Center (MHCRC) of the University of Iowa College of Medicine on the reproducibility and validity of the ICD-10 and DSM-IV clinical and operational diagnoses of schizophrenia, which clearly showed the limitations of structured diagnostic interviews for schizophrenia. This study compared clinical diagnoses made by clinicians using unstructured interviews and operational diagnoses generated from a computer algorithm derived from the Comprehensive Assessment of Symptoms and History (CASH).[6]

Background

The DSM-IV nosological concept of schizophrenia has been strongly contested by many researchers, such as, for example, Maj in 1998.[7] Schizophrenia, as defined by DSM-IV, does not follow any "classic" paradigm. It is a diagnosis by exclusion. The symptomatological, chronological, and functional criteria, taken together, are not sufficient to characterize schizophrenia as a syndrome, so that exclusion criteria are decisive for the diagnosis. What we currently call schizophrenia is merely a heterogeneous group of nonaffective psychotic syndromes whose etiology is unknown. Does the schizophrenic syndrome have a special character that cannot be translated into operational terms? Does the diagnosis of the trained psychiatrist rely on a holistic impression of the subject, which operational criteria are unable to communicate? Do DSM-IV criteria fail to catch one or more clinical aspects that are essential for the diagnosis? If all essential elements of the schizophrenic syndrome are present in the DSM-IV definition, are they described in insufficient detail? Or is the clustering of symptoms not appropriately defined?

Most databases for biological research in psychiatry are now produced with the help of structured diagnostic interviews. Structured interviews represent the mainstay of diagnostic instruments in psychiatry, particularly those which allow some freedom to follow individual leads that may emerge. They can also be programmed for computerized scoring. For example, the Schedule for Clinical Assessment in Neuropsychiatry (SCAN)[8] and Comprehensive Assessment of Symptoms and History (CASH)[9] are excellent structured interviews and recording instruments for documenting the signs, symptoms, and history of subjects evaluated in research studies on the major psychoses and affective disorders. Nevertheless, structured interviews have substantial limitations that restrict their diagnostic validity. Any diagnosis that relies on the subjective interpretation of patient reports or laboratory tests, as well as on instrumental assessment, carries some risk of error. This error may be due to the equipment used (faulty equipment, poor calibration), to human error on the part of the assessors (poor training, carelessness, mislabeled samples or reports), or to the patients (misreporting or inconsistency in what patients say or do). Almost all diagnostic procedures include one or other of these elements. Medical diagnosticians are not infallible, and probably will never be so.[9]

Structured interviews provide broad descriptive coverage in order to enable investigators to make diagnoses using a variety of criteria, but they cannot provide an appropriate instrument for making a differential diagnosis. The validity of arbitrarily constructed diagnoses can be tem-

porary only. When a disorder becomes better understood, the symptoms held to be the most reliable may well prove to lose their importance as indicators of the condition. In time, phenomenologically (arbitrarily) constructed diagnoses and clinician "gold standard" diagnoses should logically diverge. The poorer the correlation between the construct and the clinician diagnosis, the greater the probability that the construct does not reflect contemporary knowledge and should be corrected or replaced.

Aim of the study

The aim of the study was to answer the following questions: (i) Is there a satisfactory correlation between computer-processed (ie, algorithmic) ICD-10 diagnoses and clinician ("gold standard") diagnoses of schizophrenia? (ii) Is there satisfactory correlation between computer-processed (ie, algorithmic) DSM-IV diagnoses and clinician ("gold standard") diagnoses of schizophrenia? (iii) In which way does the degree of correlation affect the diagnostic validity of ICD-10 and DSM-IV schizophrenia?

Hypothesis

Assuming the expert clinician diagnosis ("holistic approach") is valid, observation of a low correlation between clinician and algorithmic diagnoses reflects the low validity of the algorithmic diagnosis.

Methods

- The medical records of 43 subjects used in the DSM-IV Field Trial Iowa Site were analyzed. DSM-IV diagnoses as well as ICD-10 diagnoses were made, using unstructured interviews (clinical expert diagnoses), and the structured, operational diagnostic (CASH) method, which records the relevant signs and symptoms (algorithmic diagnoses). To enhance the validity of the results of the unstructured psychiatric examinations, we controlled all 43 medical records with regard to the consistency of the objective medical and subjective patient data. The symptoms and syndromes listed in CASH were carefully evaluated by well-trained MHCRC specialists.
- The diagnostic algorithm was applied directly to the CASH diagnoses.
- Diagnostic algorithms were prepared for, and applied to, the DSM-IV and ICD-10 diagnoses of schizophrenia.
- Algorithmic diagnoses and expert clinician diagnoses were correlated by calculating the kappa coefficient *(Table I)*.
- Possible explanations for the observed diagnostic discordance were proposed.

Results

As can be seen in *Table I*, only a marginal correlation between expert clinician and algorithmic DSM-IV and ICD-10 diagnoses of schizophrenia was found. Assuming

● DSM-IV algorithm	Expert clinician diagnoses
kappa	0.34

● ICD-10 algorithm	Expert clinician diagnoses
kappa	0.37

kappa >0.75 ..... excellent correlation
0.4<kappa<0.74 ..... good correlation
kappa<0.4 ..... marginal correlation

Table I. Correlation between DSM-IV / ICD-10 diagnoses and expert clinician diagnoses.

the expert clinician diagnoses of schizophrenia (made by the "holistic approach") were indeed valid (the "gold standard"), the implication is that *the validity of algorithmic diagnoses was relatively low.*
Four main limitations of the arbitrarily made diagnoses of DSM-IV and ICD-10 schizophrenia were found, relating to: (i) symptom severity thresholds; (ii) evaluation of the mood syndrome; (iii) specification of psychotic/mood duration ratio; and (iv) ICD-10/DSM-IV differences in the specification of hallucinations.

Discussion

The results of the study show that instrumentally generated DSM-IV or ICD-10 diagnoses of schizophrenia had relatively low validity when compared with clinician expert diagnoses. These findings are in agreement with the views expressed by Maj in his editorial,[6] and lead to the following questions:

- Is it possible to determine whether the operational approach is disclosing the intrinsic weakness of the concept of schizophrenia or the intrinsic limitations of the operational approach?
- Is there, perhaps, beyond the individual phenomena, a "psychological whole" that the operational approach fails to grasp, or is such a "psychological whole" simply an illusion that the operational approach unveils?
- Is there a possibility that the potential of the operational approach has not been fully tapped? For example, some important "classic" features such as autism were omitted in the operational criteria of schizophrenia.
- Does the form and content of the subjective experiences of individuals who are diagnosed as having schizophrenia require more in-depth investigation and characterization, reversing the recent process of reduction of psychotic phenomena to their lowest common denominator?

What are the weak points of the DSM and ICD classifications?

After years of experience with the DSM-IV and ICD-10 classifications, some more or less anticipated weak points of these classifications have become evident. Many critical analyses have been published, eg, the recently published article by Tucker.[10] The current DSM and ICD process gives the image of precision and exactness. Indeed, we as psychiatrists have come to believe that we are dealing with clear and discrete disorders rather than arbitrary symptom clusters. We are now being taken at our own word by managed care companies that stipulate that if a patient's symptoms fulfill current criteria for schizophrenia or recurrent depressive disorder, drug treatment must be given strictly according to the textbook. In fact, to quote Gary J. Tucker "at best, we are between Scylla and Charybdis—we no longer want to say that each patient is a unique individual, nor can we honestly say that every case clearly fits diagnostic criteria."[10] All of this apparent precision overlooks the fact that, as yet, we have no identified etiological agents for psychiatric disorders. In psychiatry, no matter how scientifically and precisely we use scales to evaluate the patient's pathological symptoms, all we are really doing is simply pattern recognition. We are still only making an empirical diagnoses and not etiological ones based on disruptions of structure of function.
After these considerations I would like to briefly consider some more optimistic perspectives that I believe could positively influence psychiatric classification and nosology in the near future. New, exciting concepts and paradigms are looming on the horizon of psychiatric classification. New intellectual frameworks for psychiatry have been introduced, for example by Kandel,[11] who proposes that the genes expressed in the brain encode proteins that play important roles at specific stages of the development, maintenance, and regulation of the neural circuits that underlie behavior. Modern cognitive psychology is exploring language, perception, memory, motivation, and skilled movements in ways that are proving to be stimulating, insightful, and rigorous. The recent merger of cognitive psychology with neural science, to give birth to cognitive neuroscience, is proving to be one of the most exciting areas in biology.
Through these and others hypotheses, psychiatry is searching for a new identity and a new nosological approach. ICD-10 and DSM-IV have offered psychiatrists worldwide consensual and more or less valid diagnostic hypotheses. But now, after years of extensive use, the time has come for a critical appraisal of both classifications. A renewed involvement of psychiatry with biology and neurology is not only scientifically important, but also epitomizes the scientific competence that should be the basis for the clinical specialty of psychiatry in the near future.

As for clinical assessment, I fully agree with Tucker that the time has come to merge the empirical psychiatry of today's classification systems with the story and actual observation of the patient. Accurate observation of symptoms and the story of the patient must be included in our diagnostic processes.[9] Perhaps multiaxial classification will prove to be one of the ways out of oversimplification.

A renaissance of psychopathological research should be encouraged. Several excellent and very sophisticated tools like SCAN or CASH have already been developed, but unfortunately their interpretation and even their terminology is not identical. We should work carefully on achieving a broad international consensus on the assessment and terminology of psychological signs and symptoms, in the same way that we worked on the whole system of psychiatric classification some years ago.

I would like to conclude with a quotation from my wonderful host and coworker from Iowa, the excellent clinician and researcher Nancy Andreasen, and propose an answer to one of the questions posed by the recently deceased distinguished Danish psychiatric taxonomist and great friend of mine from Århus, Eric Strömgren.

Nancy Andreasen wrote in a very recent article[12]:

"While evidence-based decision making is a core value of medicine, and while DSM has done a valuable service in standardizing diagnostic practices, we as physicians must also devote a part of our time and energy to understanding how our patients feel and think and change subjectively. This is central to our role as doctors—if we are going to help them as healers, and if we are going to develop innovative insights about disease processes to test in research paradigms."

Eric Strömgren asked in 1992[4]: "We are carried on by a huge taxonomic wave. Returning to classification, to taxonomy, we must ask the question: Are we just now in what could be called a 'taxonomorphic' age?"

It seems to me that the right answer to Strömgren`s question today is: "Yes, we are." ❑

This study was conducted while the author was the recipient of a Fulbright Grant No. 20996. Hosts: Nancy C. Andreasen, MD, PhD; Andrew H. Woods, Professor of Psychiatry, Director, Mental Health Clinical Research Center, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, Iowa 52242, USA. Computerized algorithm for the CASH and statistical analyses was provided by Dr Beng Choon Ho. Dr Michael Flaum was the main advisor for the project design.

Validez de la clasificación nosológica

El término "clasificación nosológica" es utilizado frecuentemente en relación con los sistemas de clasificación médica y se tiende a equipararlo a "diagnóstico" y "validez". Sin embargo, especialmente en el ámbito de la psiquiatría, esto dista mucho de la realidad. Desde un punto de vista científico, los dos sistemas de clasificación hasta ahora más utilizados -el Diagnostic and Statistical Manual of Mental Disorders, *en su cuarta edición (DSM-IV) y la décima versión de la* Clasificación Internacional de las Enfermedades *(CIE-10)- pueden considerarse como la base teórica de la nosología psiquiátrica actual. En este artículo, nos proponemos demostrar que los diagnósticos de esquizofrenia del DSM-IV y de la CIE-10, concebidos de manera instrumental, poseen una validez relativamente baja en comparación con los diagnósticos establecidos por clínicos expertos. Si la clasificación médica debe ser realista, de uso simple y fiable, los sistemas nosológicos deberían no sólo establecerse sobre hechos observados sino también sobre la base de supuestos teóricos relativos a la naturaleza de la enfermedad.*

Validité de la classification nosologique

Le concept de "classification nosologique" est fréquemment utilisé en rapport avec les systèmes de classifications médicales et la tendance actuelle est de le mettre sur un pied d'égalité avec "diagnostic" et "validité". C'est pourtant loin d'être vrai dans bien des cas, en particulier dans le domaine de la psychiatrie. D'un point de vue purement scientifique, les deux systèmes de classification les plus récents utilisés de nos jours, le Diagnostic and Statistical Manual of Mental Disorders, *quatrième édition (DSM-IV) et* l'International Classification of Diseases, *dixième révision (ICD-10), peuvent être considérés comme le fondement théorique de la classification nosologique psychiatrique actuelle. Cet article souligne le fait que la validité du diagnostic de schizophrénie basé sur les critères du DSM-IV ou de l'ICD est relativement faible comparativement à celle du diagnostic basé sur l'observation clinique pure. Si une classification médicale se doit d'être réaliste, facile à utiliser et fiable, les systèmes nosologiques se doivent quant à eux d'être basés non seulement sur des faits avérés, mais également sur des hypothèses théoriques concernant la nature de la maladie.*

REFERENCES

1. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research.* Geneva, Switzerland: World Health Organization; 1993.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th edition. Washington, DC: American Psychiatric Association; 1994.
3. Strömgren E. Nosology and classification—friends or foes? In: Ferrero FP, Haynal, AE, Sartorius N, eds. *Schizophrenia and Affective Psychoses. Nosology in Contemporary Psychiatry.* London, UK: John Libbey CIC srl; 1992:11-16.
4. Lehman HE. Psychopathological evaluation and nosological conceptualisation. In: Ferrero FP, Haynal AE, Sartorius N, eds. *Schizophrenia and Affective Psychoses. Nosology in Contemporary Psychiatry.* London, UK: John Libbey CIC srl; 1992:17-25.
5. Popper KR. Alles Leben ist Problemlösen. Munich, Germany: Piper; 1994.
6. Andreasen NC. Comprehensive Assessment of Symptoms and History (CASH). MH-CRC, Department of Psychiatry University of Iowa College of Medicine, USA; 1987:155.
7. Maj M. Critique of the DSM-IV operational diagnostic criteria for schizophrenia. *Br J Psychiatry.* 1998;172:458-460.
8. World Health Organization. Schedules for Clinical Assessment in Neuropsychiatry. Version 2.0. Geneva, Switzerland: World Health Organization; 1994.
9. Kraemer HC. *Evaluating Medical Tests.* London, UK; Sage Publications; 1992: 295.
10. Tucker GJ. Putting DSM-IV in perspective. *Am J Psychiatry.* 1998;155:159-161.
11. Kandel ER. A new intellectual framework for psychiatry. *Am J Psychiatry.* 1998;155:457-469.
12. Andreasen NC. The crisis in clinical research. *Am J Psychiatry.* 1998;155:455. Editor`s Coment.

Diagnostic classification of psychiatric disorders and familial-genetic research

Wolfgang Maier, MD

The validity of diagnostic definitions in psychiatry is directly related to the extent to which their etiology can be specified. However, since detailed knowledge of causal or susceptibility factors is lacking for most psychiatric disorders with a known or suspected familial-genetic origin, the current widely accepted classification systems largely fail to achieve this ideal. To illustrate this problem, this paper looks at the difficulties posed by the criteria for schizophrenia as laid down in the International Classification of Diseases, *10th revision (ICD-10) and the* Diagnostic and Statistical Manual of Mental Disorders, *Third Edition, Revised (DSM-III-R), and highlights the discrepancies between the majority of diagnostic boundaries and the various phenotype aggregation patterns observed in family studies. Progress in our understanding of psychiatric disorders requires to be firmly based on the findings of epidemiological studies as well as on a clear appreciation of the limitations of classification tools.*

Keywords: *classification system; ICD-10; DSM-III-R; DSM-IV; genetics; family study; schizophrenia; affective disorder; schizoaffective disorder*

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Clinical diagnoses—whether in the field of psychiatry or somatic medicine—seek to delineate disease entities characterized by distinct etiologies. Since most psychiatric disorders have a familial-genetic basis, diagnostic definitions should therefore be able to delineate distinct familial-genetic pathways. The ideal situation is provided when the etiological factors (ie, the genetic mutations causing or influencing a specific disorder) are known: in this case, the definition of the disorder will be directly derived from the phenotype induced by the causal or susceptibility factor(s), with uncontroversial validity, since the definition delineates a distinct syndrome attributable to a distinct familial-genetic pathway.

However, to this day, such detailed knowledge of causal or susceptibility factors remains elusive for the vast majority of psychiatric disorders in which a familial-genetic origin is known or suspected; in fact, the only exception is represented by the subtypes of Alzheimer's disease.[1] Thus, alternative strategies need to be applied in order to formulate appropriate definitions of psychiatric disorders with a familial-genetic origin. But how in this case can one judge the validity of the competing diagnostic definitions thus derived?

Two major criteria of validity have been proposed:

- The stronger the genetic determination, the more valid the diagnostic definition; consequently, heritability estimates derived from twin studies may serve as criteria of validity.
- The stronger and more specific the familial aggregation, again, the more valid the diagnostic definition.

Diagnostic distinctions based on familial-genetic studies

The two aforementioned criteria of validity were the very ones that were used, in the past, to establish the now widely accepted classification of affective disorders that

distinguishes bipolar disorder and unipolar depression:

- Twin studies established a higher degree of heritability for bipolar disorder than for affective disorders in general.[2]
- Family studies consistently demonstrated that bipolar disorders aggregate only in families of probands with bipolar disorder, and not in families of probands with other subtypes of affective disorder.[3]

On the basis of these findings, all currently used classification systems, in particular the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Classification of Diseases* (ICD), define the now well-known diagnostic criteria for the two groups of affective disorders.

More recently, an intermediate syndrome between unipolar depression and bipolar disorder, so-called bipolar II disorder, has been defined. This condition is characterized by depressive episodes with manic states too short in duration or too mild in intensity to qualify as a manic episode. A series of family studies (eg, Dunner et al[4]) showed that bipolar II disorder followed a specific intrafamilial pattern of aggregation. Other family studies found that bipolar II disorder, but not other types of bipolar disorder, strongly aggregated in families of probands with bipolar II disorder.[5,6] However, in contrast to the Research Diagnostic Criteria (RDC), the currently most widely distributed classification systems, DSM-III-R, DSM-IV, and ICD-10, included the intermediate constellation bipolar II disorder under the heading bipolar disorder.

To further illustrate the contribution of familial-genetic studies to the classification of psychiatric disorders, this paper takes a closer look at how the aforementioned considerations have impacted on the diagnostic definitions of schizoaffective disorders.

The first criteria-based definition of this disorder was proposed by the RDC. This disorder was shown to aggregate in families, but not in a specific manner.[7] Some variants of this disorder also occurred more commonly than would be expected by chance in families of probands with schizophrenia and other variants in families of probands with affective disorders, and vice versa. The clinical characterization of these variants demonstrated that cosegregation with schizophrenia was preferentially associated with the more chronic, schizophrenia-like schizoaffective disorder, whereas other subtypes coaggregated preferentially with affective disorders.[8] As a consequence, the schizophrenia-like schizoaffective disorders were distinguished from other schizoaffective disorders, which were subsequently considered to belong to the affective disorders in DSM-III-R and DSM-IV and likewise in ICD-10.

Diagnostic definitions ignoring familial-genetic evidence

Several studies were recently conducted applying one of the aforementioned criteria of validity to competing diagnostic definitions or diagnostic criteria, particularly with regard to the definition of schizophrenia and psychotic disorders. Twin and family studies focused primarily on the positive/negative distinction. It was demonstrated that the complex of negative symptoms was fairly consistently associated with a high familial similarity, a higher familial loading with psychotic disorders, and a higher genetic load than positive symptoms.[9]

One twin study even found no genetic influence at all on the occurrence of positive symptoms (first-rank Schneiderian symptoms), whereas other definitions, including positive and negative symptoms in the definition of schizophrenia, were associated with at least a moderate degree of heritability.[10] If a classification system relies on the specificity and magnitude of underlying genetic determinants, a redefinition of the concepts of schizophrenia and other psychotic disorders should result from these findings. In contrast to this empirical evidence, even the most recent definitions of schizophrenia and psychotic disorders in DSM-III-R, DSM-IV, and ICD-10 give priority to positive symptoms. As an exception, ICD-10 proposes the residual category of latent schizophrenia (schizophrenia simplex), which is only defined by the presence of negative symptoms, in the absence of positive symptoms. The familial-genetic nature of this condition is not widely known, as most research into the genetics of schizophrenia is based on cases with a mixture of positive and negative symptoms. The most distinctive difference between the DSM-III-R, DSM-IV, and ICD-10 classification of schizophrenia is the minimal duration of the disease episodes. ICD-10 requires the presence of symptoms for just 1 month. DSM-III-R and DSM-IV require 6 months, and consider psychotic patients meeting the symptom criteria for schizophrenia for less than 6 months to belong to the category of schizophreniform disorders. Several studies have shown that the course of schizophrenia

(including episode duration) is independent of the familial loading.[11] Given this body of evidence, a differential validity of the ICD-10 and DSM-III-R and DSM-IV definitions of schizophrenia is unlikely. In keeping with this expectation, we found in a family study[12] a similar degree of familial aggregation of schizophrenia as defined by DSM-III-R and DSM-IV or ICD-10, although the prevalence rates were very different *(Table I)*.

The degree of familial aggregation is indicated by the odds ratios (OR) with 1.0 indicating the risk in the general population and values higher than with 1.0 indicating the degree of increased risk with respect to the general population. A similar degree of familial aggregation is apparent for DSM-III-R and ICD-10 in *Table I*, although a difference in criteria for minimal episode duration may result in differences in cumulative lifetime prevalence rates.

Diagnosis of schizophrenia in relatives of schizophrenics	Lifetime prevalence rates		Relative risk (OR) [95% confidence interval]
	Relatives of probands with schizophrenia (ICD-10: n=620,DSM-III-R: n=485)	Relatives of general population probands (n = 500)	
by ICD-10	6.5%	0.9%	7.1
			[3.5; 11.9]
by DSM-III-R	3.0%	0.5%	6.0
			[2.0; 12.0]

Table I. Cumulative lifetime prevalence rates for schizophrenia: first-degree relatives of probands with schizophrenia by two diagnostic systems. Abbreviations: DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders,* Revised Third Edition; ICD-10, *International Classification of Diseases,* 10th Revision; OR, odds ratio.

In conclusion, although DSM-III-R and ICD-10 have different definitions for schizophrenia, these differences have no relevant impact on the degree of familial aggregation.

Spectrum of conditions defining the familial phenotype as exemplified by schizophrenia

Another strategy to explore the boundaries of a familial disorder is to delineate the range of syndromes and durations coaggregating with schizophrenia in families. This strategy is particularly informative if relatives of schizophrenics who are likely to have a genetic vulnerability to schizophrenia (so-called obligate carriers) are investigated. Obligate carriers are relatives of schizophrenics located in the pedigree between two cases with schizophrenia, eg, the mother of a schizophrenic index case is considered to be an obligate carrier if one of her siblings or one of her parents was also suffering from schizophrenia or another psychotic disorder (independently of the phenotype of the mother of the index case). As the familial aggregation of schizophrenia is unlikely to be due to random variation (because of the low prevalence rate in the general population), or nongenetic familial factors (as evidenced by twin studies), the only remaining possibility is genetic factors. Thus, differences in the prevalence of obligate carriers of disorders, syndromes, and behavioral deviations in families of schizophrenics are likely to be expressed by the genetic diathesis of schizophrenia.

Table II shows the cumulative lifetime prevalences of psychiatric disorders (DSM-III-R) for obligate carriers identified in our aforementioned family study.[12] The excess of diagnosis-specific prevalence rates is only significant for two groups of disorders (due to sample size limitation). It is apparent that the genetic vulnerability to schizophrenia is not only expressed as schizophrenia. These findings are in keeping with those of another series of family studies, which showed that all variants of nonaffective psychotic disorders (schizotypal personality disorders and schizoaffective disorders) cosegregated with schizophrenia.[13]

Similarly, some family studies reported an excess of affective disorders (particularly psychotic affective disorders) in subjects at elevated risk for schizophrenia. In addition, one series of family studies[12] demonstrated that

	Obligate carriers (n=41)	Matched controls (n=41)
Schizophrenia/ schizophreniform disorders	8.2%	0.9%*
Schizoaffective disorders	1.2%	0%
Other nonaffective psychoses (including schizotypal personality disorders)	2.3%	1.1%
Psychotic affective disorders	3.0%	1.0%
Nonpsychotic affective disorders	18.0%	9.1%*
Other psychiatric disorders	20.9%	18.4%

Table II. Lifetime prevalences in relatives of schizophrenics (obligate carriers) and controls. *$P \leq 0.05$.

a heterogeneous collection of deviations (eg, personality deviations not qualifying as a disorder, neuropsychological deficits) might also develop as a consequence of an increased risk for schizophrenia. Thus, the range of the phenotype transmitted in families of schizophrenics is not at all identical to the diagnostic boundaries proposed by any diagnostic manual.

On the other hand, there is also evidence that specific subtypes of schizophrenia aggregate in families with a very specific pattern of aggregation. Recently, Beckmann et al[14] demonstrated that periodic catatonia defined a homogeneous familial aggregation pattern. However, this specific psychotic syndrome is only remotely associated with the catatonic subtype of schizophrenia defined by ICD-10 and DSM-III-R. Taken together, the diagnostic distinctions and boundaries defined by ICD-10 and DSM-III-R are not compatible with the phenotype of schizophrenia transmitted in families, although these diagnostic categories were shown to be familial and under genetic control.

Diagnostic definitions and linkage studies

Consequently, it is not surprising that linkage studies tracing the localization of susceptibility genes for a specific psychiatric disorder have failed to reveal a specific relationship to diagnostic categories. Two examples of this are discussed in the following.

- One replicated linkage finding in schizophrenia is on 6p.[15] Maximal logarithm of the odds of linkage (LOD) scores indicate the strength of cosegregation of genetic markers and the disease. Comparison of the maximal LOD scores across diagnostic definitions (by DSM-III-R), varying by restrictiveness, revealed maximal diagnosis-specific LOD scores for the broadest definition including all variants of psychotic disorders; the maximal LOD score for narrowly defined schizophrenia was substantially lower.
- Several candidate regions in the genome are likely to host susceptibility genes for bipolar affective disorders. One of these regions is 18p. A suggested linkage to bipolar disorder was found by several independent linkage studies in bipolar disorder. Recently, Schwab et al[16] also found suggested linkage for schizophrenia to the same pericentromeric candidate region. In addition, the diagnosis-specific maximal LOD score was substantially increased by including not only schizophrenia and schizoaffective disorders in the phenotype, but also affective disorders.

Conclusion

These two examples highlight the limited value of the currently most widely accepted diagnostic definitions of psychotic disorders for the identification of specific genetic vulnerabilities. However, there is currently no other option to the diagnosis-based linkage and association approach to localize disease genes. The limited validity of diagnostic definitions and their putative loose relationship to specific genetic vulnerabilities have to be compensated for by extension of sample size. Once the first susceptibility genes have been detected, more specific genotype–phenotype relationships can be identified. ❑

Clasificación diagnóstica e investigación familiar y genética en los trastornos psiquiátricos

La validez de las definiciones diagnósticas en psiquiatría se relaciona directamente con la posibilidad de especificar su etiología. Ya que se carece de un conocimiento detallado de la etiología o de los factores de susceptibilidad de gran parte de los trastornos psiquiátricos con un origen familiar-genético, conocido o sospechado, los sistemas clasificatorios actuales no permiten conseguir este objetivo. Con el fin de ilustrar este problema, el presente artículo examina las dificultades planteadas por los criterios de esquizofrenia establecidos en la Clasificación Internacional de Enfermedades *en su décima versión (CIE-10) y en el* Diagnostic and Statistical Manual of Mental Disorders, *en su tercera edición revisada (DSM-III-R). Se destacan las discrepancias entre la mayoría de los límites diagnósticos y los diversos modelos de agregación fenotípica observados en estudios familiares. El progreso en la comprensión de los trastornos psiquiátricos requierede una base firme en los hallazgos de los estudios epidemiológicos como también en una apreciación clara de las limitaciones de los instrumentos clasificatorios.*

Classification diagnostique et recherche sur l'étiologie familiale/génétique des maladies psychiatriques

*La validité des définitions diagnostiques en psychiatrie est directement liée à la possibilité de spécifier l'étiologie des maladies concernées. Or, à partir du moment où pour la plupart des maladies psychiatriques, avec une origine génétique connue ou suspectée, on ne connaît que peu les facteurs causaux ou prédisposants, les classifications actuelles, largement acceptées, ne permettent généralement pas de remplir cet objectif. Cet article illustre ce problème à travers les difficultés rencontrées avec les critères de la schizophrénie de l'*International Classification of Diseases, *10e révision, du* Diagnostic and Statistical Manual of Mental Disorders, *3e édition révisée (DSM-III-R). L'auteur souligne à quel point le fossé est grand entre la plupart des entités diagnostiques et les divers modèles phénotypiques observés dans les études familiales. Si notre progression dans la compréhension des troubles psychiatriques doit se fonder sur les résultats des études épidémiologiques, il faut garder à l'esprit les limites des outils de classification qui sont à notre disposition.*

REFERENCES

1. Blacker D, Tanzi RE. The genetics of Alzheimer disease: current status and future prospects. *Arch Neurol.* 1998;55:294-296.
2. Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Arch Gen Psychiatry.* 1986;43:923-929.
3. Rice J, Reich T, Andreasen NC, et al. The familial transmission of bipolar illness. *Arch Gen Psychiatry.* 1987;44:441-447.
4. Dunner DL, Gershon ES, Goodwin FK. Heritable factors in the severity of affective illness. *Biol Psychiatry.* 1976;11:31-42.
5. Heun R, Maier W. The distinction of bipolar II disorders from bipolar I and recurrent unipolar depression: results of a controlled family study. *Acta Psychiatr Scand.* 1993;87:279-284.
6. Coryell W, Endicott J, Reich T, Andreasen N, Keller M. A family study of bipolar II disorders. *Br J Psychiatry.* 1984;145:49-54.
7. Maier W, Lichtermann D, Minges J, Hein R, Hallmayer J, Benkert O. Schizoaffective disorder and affective disorders with mood-incongruent psychotic features: keep separate or combine? Evidence from a family study. *Am J Psychiatry.* 1992;149:1666-1673.
8. Baron M, Gruen R, Asnis L, Kane J. Schizoaffective illness, schizophrenia and affective disorders: morbidity risk and genetic transmission. *Acta Psychiatr Scand.* 1982;65:253-262.
9. Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic-epidemiologic perspective. *Schizophr Bull.* 1993;19:261-285.
10. Farmer AE, McGuffin P, Gottesman II. Twin concordance for DSM-III schizophrenia: scrutinising the validity of the definition. *Arch Gen Psychiatry.* 1987;44:634-641.
11. Kendler KS, Tsuang MT. Outcome and familial psychopathology in schizophrenia. *Arch Gen Psychiatry.* 1988;45:338-346.
12. Maier W, Lichtermann D, Minges J, et al. Continuity and discontinuity of affective disorders and schizophrenia. *Arch Gen Psychiatry.* 1993;50:871-883.
13. Kendler KS, McGuire M, Gruenberg AM, Spellman M, O'Hare A, Walsh D. The Roscommon family study. II. The risk of nonschizophrenic nonaffective psychoses in relatives. *Arch Gen Psychiatry.* 1993;50:645-652.
14. Beckmann H, Franzek E, Stöber G. Genetic heterogeneity in catatonic schizophrenia: a family genetic study. *Am J Med Genet.* 1996;67:289-300.
15. Straub RE, MacLean CJ, O'Neill FO, et al. A potential vulnerability locus for schizophrenia in chromosome 6p24-22: evidence for genetic heterogeneity. *Nat Genet.* 1995;11:287-293.
16. Schwab SG, Hallmayer J, Lerer B, et al. Support for a chromosome 18p locus conferring susceptibility to functional psychoses in families with schizophrenia, by association and linkage analysis. *Am J Hum Genet.* 1998;63:1139-1152.

Letters to the Editor

Re: Bipolar Disorders Issue

Preliminary evidence for an association of a G-protein-β_3–gene variant with bipolar disorder—The signal transduction pathway is gaining increasing importance both with respect to the understanding of the neurobiological basis of bipolar disorders and as a possible target for antidepressant action.[1] G-proteins in particular, which convey the signals from receptor to effector proteins, are key elements in the regulation of cellular responses, such as the increase in intracellular calcium ion concentration $[Ca^{2+}]_i$, an early event of the signal transduction cascade. One of the most consistent findings in bipolar patients has been the observation of increased $[Ca^{2+}]_i$ in the peripheral cells of acute manic patients, which is downregulated to normal after successful treatment.[2] The recently identified variant of a G-protein-β_3 subunit ($G\beta_3$-s) has been shown to be associated not only with hypertension, but also with increased signal transduction and ion transport activity.[3] In the preliminary study we briefly report on here, we investigated whether the functionally active variant $G\beta_3$-s was more abundant in patients with bipolar disorder than in controls. We further examined whether the $G\beta_3$-s allele was associated with an increase in calcium ion stimulation in lymphoblasts.

Genomic DNA of 111 healthy controls (56 females, 55 males) and 19 patients with bipolar disorder (euthymic at the time of investigation; 9 females, 10 males) was genotyped for the $G\beta_3$ variant (= T allele). In our controls, the T allele frequency (0.28) closely matches that found in the literature (0.25).[4] However, in bipolar patients, the T allele (associated with enhanced G-protein activity) was more frequent *(Table)*.

When the TT and TC genotypes were analyzed together (which seems justified, since the phenotype is apparently not different), the difference between bipolar patients and controls was significantly different (Fisher exact test, P=0.049).

Assessment of the $[Ca^{2+}]_i$ response, stimulated via $G\beta_3$-s in lymphoblasts of 14 controls and 12 patients, showed that the presence of the T allele (heterozygous or homozygous) leads to an overall increase in calcium response after platelet-activating factor (PAF) stimulation (C, 485±109 nM; T, 761±321 nM; P=0.019), whereas basal levels are unaffected (C, 76±33 nM; T, 87±29 nM; NS). No significant difference was found between euthymic bipolar patients and controls, although stimulated $[Ca^{2+}]_i$ values were higher in bipolar patients (648±348 nM) than in controls (537±189 nM).

Although our results are preliminary and need to be confirmed in a large sample, they suggest that genetic variants in genes of the transduction pathway could contribute to the increased calcium concentration and increased signal transduction reported during acute manic episodes, thus supporting the calcium-related theory of Dubovsky and coworkers.[5] Several adaptative mechanisms may account for the more or less balanced calcium homeostasis observed during and after successful treatment. This, however remains to be elucidated in detail.

Probands	T/T	T/C	C/C	Frequency T	Frequency C	Fisher exact test
Controls (n=111)	8	46	57	0.28	0.72	
Bipolar patients (n=19)	2	12	5	0.42*	0.58	P=0.049

Table. Genotypes and allele frequencies of controls and bipolar patients.

REFERENCES

1. Rasenick MM, Chaney KA, Chen J. G-protein–mediated signal transduction as a target of antidepressant and antibipolar drug action: evidence from model systems. *J Clin Psychiatry.* 1996;57(suppl 13):49-55.
2. Yatham LN, Srisurapanont M, Zis AP, Kusumakar V. Comparative studies of the biological distinction between unipolar and bipolar depression. *Life Sci.* 1997;61:1445-1455.
3. Siffert W, Rosskopf D, Siffert G, et al. Association of human G-protein-beta 3 subunit variant with hypertension. *Nat Genet.* 1998;18:45-48.
4. Siffert W. G-proteins and hypertension: an alternative candidate gene approach. *Kidney Int.* 1998;53:1466-1470.
5. Dubovsky SL, Murphy J, Thomas M, Rademacher J. Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. *Am J Psychiatry.* 1992;149:118-120.

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Letters to the Editor

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