Eur Arch Psychiatr Neurol Sci (1989) 238:280–284

European Archives of Psychiatry and Neurological Sciences

The Interface of Clinical Psychopharmacology and Psychopathology

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Summary. Four areas of common interest for clinical psychopharmacology and psychopathology are identified: (1) the diagnostic-based approach in clinical psychopharmacology; (2) the characterization of psychotropic drugs according the main psychopathologically defined target symptoms; (3) prediction of treatment response; (4) development of rating scales. The current state of research strategies in these areas is discussed and the need for new strategies is stressed. In particular, diagnosis-based research strategies in clinical psychopharmacology are not fully justified by empirical data; an alternative approach is discussed.

Key words: Psychopharmacology – Psychopathology

Introduction

The rapid development of clinical psychopharmacology in the last three decades has decisively influenced clinical psychopathology: rating scales – first developed for the assessment of the clinical efficacy of psychotropic drugs – became the methodological guideline for new approaches in describing and classifying psychopathological symptomatology. Thus a "pharmacological dissection" (Klein 1964) was the basis for a new psychopathological and diagnostic category labelled "panic disorder". On the other hand, clinical psychopharmacology relies on psychopathological principles: the classical psychopathological distinction between anxiety, depression, schizophrenia and organic brain syndromes is used as the major basis for the taxonomy (anxiolytics, antidepressants, neuroleptics, nootropics). In spite of being not validated for its use in psychopharmacology this classificatory principle is widely accepted.

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Parts of this article were presented on the occasion of the inauguration ceremony of the Department of Psychiatry of the University of Mainz on April 2 and 3, 1987

Besides these positive interactions between both fields of psychiatric research negative interactions cannot be ruled out. Diagnostic decisions based on psychopathological symptoms are the basis for the choice between different kinds of psychotropic drugs; the predictive power of diagnostic schedules has, however, not so far been convincingly established. The distinction between antidepressant, anxiolytic, neuroleptic and nootropic efficacy (derived from psychopathological symptomatology) may preclude the development of new drugs which have a psychotropic efficacy and are clinically useful but do not fit any of these categories.

These positive and negative interactions have stimulated a methodological discussion on the optimal coordination of both fields of psychiatric research in order to overcome the limitations and to increase the progress in clinical psychiatry. We will focus this discussion on four major problems.

Psychopathologically Defined Diagnoses as Guidelines for the Application of Drugs and as Selection Criteria for Drug Studies

According to a classical principle in medicine diagnoses serve as guidelines for deciding between alternative treatments. This principle has been useful in psychiatry too: the diagnoses of "schizoaffective" disorders was mainly derived from psychopathological concepts; most of these patients have previously been diagnosed as "schizophrenics" and have been exclusively treated with neuroleptic drugs at least in the United States; after the schizoaffective disorders were precisely described by the research diagnostic criteria (RDC; Spitzer et al. 1975a) most of these patients received a prophylactic long-term treatment with lithium; most of these patients did better with lithium than under long-term treatment with neuroleptics (Pope and Lipinski 1978).

Psychopathologically defined diagnoses also benefit from clinical psychopharmacology: Klein first treated not only depressive but also anxiety disorders with imipramine; some of the patients with anxiety disorders also improved under imipramine; these patients were characterized by panic attacks, whereas patients with generalized anxiety without panic attacks had less benefit from imipramine (Klein 1964). The relevance of this result was not recognized by psychopathologist for a long time; the first diagnostic system proposing a special category of panic disorder was the RDC; since this time anxiety disorders have been subdivided into panic, phobic and generalized anxiety disorders.

The advent of operationalized diagnostic criteria (e.g. RDC, DSM-III) for classifying patients and of well-designed assessment systems for psychopathology was of great importance for clinical psychopharmacology. The reliability of diagnostic allocations for the selection of patients and of the assessment of treatment response was increased significantly in this way. Therefore the amount of non-informative variance and the between-centres variation were reduced; multi-centre trials became feasible in this way. More precise and objective conclusions from drugs trials could be drawn.

However, intended areas of indications described in diagnostic terms and the ranges of efficacy of psychotropic drugs are not in a one-to-one relationship. This can best be demonstrated using the example of antidepressant drugs. They were originally intended to treat endogenous depressions and were only rarely tested for their efficacy in other subtypes of depression; later on it turned out that tricyclic antidepressants are only of limited use for delusional depressions (Spiker et al. 1985) and that they are effective for the several non-endogenous subtypes of major depression (Stewart et al. 1983). Mild depressions cannot be effectively treated with tricyclic antidepressants according to a recent study (Paykel et al. 1988). These facts demonstrate that sticking to diagnostic "ideologies" slows down the development of sound and effective treatment schedules.

There are other examples demonstrating that the useful application of particular drugs is not limited to certain diagnostic classes; effective treatment of stupor is possible with the benzodiazepine lorazepam (Wetzel et al. 1987). Equally, the neuroleptic drug sulpiride also works as an antidepressant (Benkert and Holsboer 1984). Lithium and carbamazepine are used not only as an efficient treatment of affective psychosis but seem to be effective in other episodic disorders, too.

These examples demonstrate that at least some psychotropic drugs are effective even beyond their original area of indication; most of these findings were made by chance and have not been replicated in methodologically sound studies. The reason is that clinical psychopharmacology remains adherent to psychopathologically defined diagnostic boundaries. It is unknown whether the range of efficacy of particular drugs can really be described in terms of psychopathologically defined diagnoses.

Praag et al. (1987) have discussed an alternative strategy to the diagnostic approach in all fields of biological psychiatry; instead of sticking to particular diagnostic categories, patients with a broad variety of diagnoses should be included in the samples under study; their psychopathological features should be described by a battery of items and factors; these psychopathological variables should then be correlated with biological characteristics. The authors call this approach "denosologization of biological psychiatry" and give evidence of its superiority over the diagnosis-based approach in some fields of psychiatric research. This strategy is similar to that proposed by Buchsbaum and Haier (1983), aiming at the inversion of dependent and independent variables. It should be kept in mind that clinical diagnoses are to be considered as conventions mainly supported by the acceptance they have received by clinicians and validated only by a small body of empirical data; they are far from being perfect, also from a psychopathological point of view. In their modern version as operationalized diagnostic discriminations they may in addition be considered as hypotheses (Klerman 1983) which will require much empirical support in the future. Psychopathological concepts ignoring clearly defined diagnostic boundaries are not in contradiction to empirial psychopathological data, as derived from the classical hypothesis of "unitary psychosis" (Griesinger 1867) or continuum models (Angst et al. 1983; Angst and Dobler-Mikola 1985; Crow 1986). From this point of view it makes little sense to consider diagnostic categories as a sound and unquestionable basis for biological research and for clinical psychopharmacology.

These arguments should stimulate strategies of a systematic investigation of the efficacy of psychotropic drugs beyond the diagnostic categories for which they are originally intended. Psychotropic drugs with antidepressive or anxiolytic or antipsychotic efficacy in preclinical trials should be tested in a whole range of major psychoses. Carefully designed assessment instruments of psychopathology and classification should be administered. Controlled clinical trials should therefore be performed in large samples including several diagnostic categories (e.g. depression and anxiety); the sample should be large enough to test diagnostic distinctions (e.g. between affective

disorders and negative schizophrenia) for their predictive power with regard to treatment outcome. This procedure also allows the definition in psychopathological terms of the range of efficacy of psychotropic drugs independent of diagnostic conventions; the utility of classification schedules can be tested in this way. Probably it will turn out for at least some psycho tropic drugs demonstrating on antidepressant pattern in preclinical trials that the clinical efficacy is not limited to depression and not observable for all subtypes of depression. The treatment of those syndromes which cannot be treated effectively up to now (e.g. negative schizophrenia) may significantly improve in this way.

Characterizing Psychotropic Drugs

The empirical support for the discrimination between different classes of psychotropic drugs is weak. This difficulty becomes evident by the differentiation between antidepressive and anxiolytic drugs. This distinction presupposes a psychopathological distinction between depression and anxiety. Empirical research in psychopathology has, however, not been able to establish a clear dissection between the two syndromes; the discrimination between depression and generalized anxiety, in particular, cannot be made in a convincing manner (Angst and Dobler-Mikola 1985). Because of the addiction to the postulate that depression and anxiety can be discriminated by clinical judgement antidepressants have not been tested for their efficacy in generalized anxiety. Only recently, several studies have addressed this question and found tricyclic antidepressants effective in treating generalized anxiety (Kahn et al. 1987). This result is an argument against making a sharp distinction between antidepressant and anxiolytic drugs.

But also the category of anxiolytic drugs has become a questionable category. After the distinction between panic, phobic and generalized anxiety disorder became familiar, the diagnostic category of anxiety disorder (neurosis) was considered to be of only limited validity. Drug trials in anxiety syndromes presently are focusing on each of the three anxiety disorders separately. It has been observed that some frequently used benzodiazepines are not effective in all three of the anxiety disorders: e.g. diazepam turned out to be ineffective in panic disorder, whereas this drug is effective in generalized anxiety disorder (Sheehan et al. 1984). This observation suggests a discrimination between antipanic drugs and drugs for treating generalized anxiety. Consequently the term "anxiolytic drug" is misleading and may perhaps prevent an optimal treatment of patients with anxiety disorders.

Prediction of Treatment Response

Criteria for the indication of specific treatments should be able to predict the response to the indicated treatment. The crucial status of psychopathologically defined diagnoses for the indication of specific treatments (e.g. antidepressant drugs for depressive disorders) can only be justified if the response to the indicated treatment can be predicted. Empirical studies demonstrating that the diagnosis of depression (major or endogenous depression) is a predictor of a more favourable response to antidepressants than to neuroleptics are not available; there is no convincing evidence that the diagnosis of schizophrenia predicts a more favourable response to neuroleptics than to antidepressants. On the other hand, several studies have indicated that some tricyclic antidepressants work in particular subtypes of anxiety disorders as well as benzodiazepines.

In order to overcome this problem studies randomly assigning neuroleptics or antidepressants to patients with affective and psychotic disorders are necessary. Unfortunately this kind of study raises ethical concerns: for affective disorders and for schizophrenic disorders treatments are available that are considered to be efficacious; therefore, the application of drugs with questionable efficacy needs ethical justification. This kind of study would be able to detect subtypes of disorders that respond more favourably to those drugs which have not been indicated up to now: e.g. antidepressant drugs may be more effective in treating negative schizophrenia than neuroleptic drugs. The only recent study of this kind has been published by Johnstone et al. (1988). They compared the effect of the antipsychotic pimozide, lithium and a combination of the two with that of placebo in a 4-week trial in 120 psychotic patients. This sample size is, however, not large enough to test the predictive power of certain psychopathological symptoms.

Many studies have tried to find psychopathological variables predicting favourable treatment response. Only a single finding in the treatment of depression could be reproduced several times: psychotic depression has a more unfavourable response to tricyclic antidepressant drugs alone than non-psychotic depression; the treatment of psychotic depression benefits if a neuroleptic drug is added; this is at least the case if the treatment period under study is not longer than 4 weeks (Spiker et al. 1985). None of the other studies with psychopathological variables have

found predictors which have remained stable in the majority of replication studies; in particular, endogenous depression has not been found to be a stable predictor of a favourable response to tricyclic antidepressants (Maier et al. 1988c).

This lack of valid psychopathological baseline predictors has motivated studies testing the predictive power of the psychopathologically defined response during the first few days; the patient's rating of early response turned out to be predictive for the final response in treating schizophrenia with neuroleptics (v. Putten and May 1978). However, it is so far unclear whether the specific pharmacological response is predicted or if this finding only reflects an association with unspecific factors (e.g. with compliance) which are relevant during the trial; in this case these variables are, in spite of their practical relevance, more a kind of early indicator of "self-predicting variable" than valid predictors. It is especially unclear up to now to what extent they reflect compliance and patients' acceptance instead of predicting efficacy for specific syndromes.

The studies proposed in the previous sections randomly allocating patients with a broad range of diagnosis to various treatments (e.g. antidepressants, neuroleptics) have the highest chance of finding predictors for response to specific treatments. Using comprehensive psychopathological inventories and/or a polydiagnostic approach may help to find stable, psychopathologically defined subtypes with predictive power. The most widely used diagnostic schedules (e.g. DSM-III) will probably not provide the most predictive subtypes (Maier et al. 1988c).

Measurement of Treatment-Response

A specific psychopathological impairment is the target symptomatology for treatment with psychotropic drugs. During treatment a broad range of changes in the psychopathological features takes place; therefore, a differentation between responders and non-responders is not precise enough. Rating scales are therefore used to quantify the severity of the symptoms combining the severity assessment of different symptoms (items), which constitute the syndrome to be treated. Rating scales are psychometric constructs which should fulfill several requirements: they should be reliable; they should be specific for the syndrome to be treated; they should be sensitive enough to detect real changes in the severity of the syndrome to be treated.

The rating scales available for the assessment of anxiety and depression do not fulfill these conditions satisfactorily (Maier and Benkert 1987; Maier et al. 1988a, b); rating scales for the assessment of schizophrenic disorders have not been sufficiently tested for these criteria.

The flaws of the rating scales show the need to look for alternative methods for measuring the severity of the psychopathological symptomatology. Monitoring methods for autonomic functions, speech behaviour and other motor functions have recently been developed. These measures have the advantage of being independent of the observer's or the patient's judgement. Studies testing the validity of these methods have been rare to date. However, the monitoring methods developed only tap some of the aspects of psychopathology. Therefore, rating scales are still needed.

Perspectives

Clinical psychopharmacology can not so far identify biological predictors for treatment response. Therefore, psychopathology is the basis for indication of treatment, assessment of treatment response and selection of patients for drug trials. However, the relationship between the two areas of psychiatric research is not clear. It has been shown that sticking to diagnostic conventions and to classical psychopathological assessment systems limits the progress in psychopharmacology.

Our concluding suggestions are for:

1. Testing the efficacy of psychotropic drugs beyond their ranges of indication.

2. Increasing the scientific efforts for studies on prediction of treatment response, testing the predictive power of psychopathological and biological variables (including family history data).

3. Testing new methods for the assessment of treatment response (monitoring autonomic and motor functions) and improving the validity of rating scales.

4. Using alternative research strategies for the empirical development of subtypes of disorders, the most important strategy has been proposed by Buchsbaum and Haier (1983); the first step should go beyond the psychopathological concepts by defining the patient's response by biological variables (e.g. receptor functions); in a second step psychopathological variables should be selected with a high correlation with the most valid biological variables; the biological and psychopathological variables selected in this way can be tested with regard to their predictive power for treatment response.

Performing research in clinical psychopharmacology beyond the bounderies of psychiatric classification

will not only contribute to knowledge in psychopharmacology. We have tried to show in this paper that clinical psychopathology will also benefit from this procedure.

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Received August 13, 1988