CHAPTER 18

Research Methodology in Clinical Trials of Psychotropic Drugs

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A. General Principles for the Clinical Investigation of Psychotropic Drugs

I. Introduction

Compared to the assessment of pharmacological effects on body functions, clinical testing of psychotropic drugs presents us with particular problems. The treatment objective, namely to influence psychiatric syndromes, is on a higher level of complexity than the goals of other pharmacotherapy, e.g., reduction of blood pressure or regulation of blood sugar level. Psychiatric syndromes can only be defined descriptively and can be distinguished from the personality of the patient, who must be treated as a whole, only by means of rough schematization. Therefore, the first step in the clinical investigation of psychotropic drugs is to bring to mind the different levels on which psychiatric syndromes can be quantified and the corresponding methods which can be used for this purpose.

The treatment targets, namely structures of the central nervous system and their conditions of functioning, are highly complex. Functional drug effects which have been experimentally demonstrated on certain animal brain structures cannot simply be transposed to human circumstances when the effect of the preparations is to be judged on the level of behavior and experience, i.e., the desired effects on man. Recent studies of the direct behavioral and experiential effects of psychotropic drugs on healthy volunteers using precise psychological methods show that these effects depend not only on the substance administered and on its dosage, but also on other factors which must be considered in the evaluation of a preparation. It is in this connection that the differences between the initial psychophysiological condition of healthy subjects and that of psychiatric patients must receive special consideration. Only under this aspect can the problem of the specificity of a psychotropic effect and its generalizability be discussed. For example, can psychiatric syndromes be reliably distinguished at the symptom level? Does a certain psychotropic substance affect a particular symptom or a certain group of symptoms, so that we can precisely delineate the specificity of this psychotropic effect? Or can the psychotropic effect of a drug only be vaguely differentiated from a nonspecific placebo effect? In contrast to other fields of pharmacology, the main and side effects of psychotropic agents cannot always be clearly discriminated.

After a thorough consideration of the special problems posed by the testing of psychiatric drugs on patients, we discuss the currently accepted strategy of clinical testing.

In a third section, we give critical attention to a number of factors responsible for the fact that precise differences in effect between various psychotropic drugs can only
be reliably proven on a very gross level. Certain factors, whose investigation must remain the subject of further research, prevent the precise determination and reliable, differentiated proof of these differences.

II. Methods for the Assessment of Psychiatric Disorders

At present, psychiatric syndromes can in principle be measured at five different levels.
1. Level of diagnosis (diagnostic entities)
2. Syndrome level (nosological nonspecificity)
3. Level of single symptoms or characteristics (nosological and syndrome nonspecificity)
4. Level of psychophysiological reactivity
5. Level of clinical-biochemical methods of investigation.

These different levels of measurement must be considered in clinical trials, although their specific meaning for the effects of psychotropic substances is presently unclear. They play a particular role in the discussion of homogeneity of sample populations. For example, it is not sufficient to characterize the subjects of a test on the diagnostic level alone. It has been shown that the effects of psychotropic medication do not restrict themselves to nosological categories. Nevertheless, it is necessary to specify the patients in a testing sample diagnostically. For this purpose, it has become customary to use the WHO classification (ICD) (DEGWITZ et al., 1980). For particular research purposes, the diagnostic criteria of FEIGHNER et al. (1972) have proved useful.

Of particular importance for the characterization of a test sample is the syndrome level. Psychiatric syndromes can be defined in various ways. One can employ the classical clinical-descriptive method and specify a syndrome diagnosis in addition to the nosological diagnosis. For example: endogenous depression, agitated or inhibited syndrome. More often, syndromes are determined by factor analysis as a means of secondary quantification of behavior characteristics. Pathological behavior is described and quantified for single characteristics using rating scales. Syndromes are then validated on large samples of psychiatric patients by means of factor analysis. Examples of such rating scales are those of LORR (1963), OVERALL and GORHAM (1962), or WITTENBORN (1955). For the description of depressive syndromes, HAMILTON’s (1960) scale is most often used. A summary of the most frequently used scales for the description of samples on the syndrome or symptom level can be found in CIPS (1977).

Symptom measurement in the classical clinical sense is the basis of the AMP system (ANGST et al., 1969). In contrast to the rating scales already mentioned, this system is based on the precise definition of traditional psychiatric symptoms and arranges them according to clinical aspects. Factor analysis has also been used to define syndromes in the AMP system. These essentially correspond to the well-known psychiatric-clinical syndromes (compare BAUMANN, 1974; PIETZCKER et al., 1977; SULZ-BLUME et al., 1979).

These first three levels in the clinical assessment of psychiatric syndromes make it clear that any quantification necessary for the analysis of a therapeutic effect is based on an abstraction. At the root of the measurement lies the relationship of the observer to the patient and the description of the patient’s observed behavior or mood within this context. Only secondarily, by means of consensual definition, can units of