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Methodology and Pitfalls in Clinical Testing of Psychopharmacological Drugs

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In 1953, with the successful introduction of chlorpromazine in the treatment of psychiatric patients, a new psychopharmacologic era was opened in psychiatric history. Around the same time, the beneficial effect of the Rauwolfia alkaloid, reserpine, in certain psychotic conditions was established, then the antidepressant properties of some monoamine oxidase inhibitor drugs (e.g. iproniazid, etc.) and of some of the iminodibenzyl derivatives (imipramine, etc.). This new era is also characterized by the increasing number of chemicals with possible psychoactive properties awaiting clinical testing.

Is this demand for clinical evaluation of psychotropic drugs of only recent origin or has it occurred before? In January 1904 the following was written editorially in the *Journal of Mental Science:* 'Analytic and synthetic chemistry are daily placing in the hands of physicians innumerable new compounds, the physiological action of which has been to a certain extent demonstrated and their beneficial effect, in diseased conditions, testified to by more or less scientific medical authorities' (4). And also in the same paper: 'The asylum clinician has such great advantages in regard to the observation of the action of these medicaments, that it is a neglect of opportunity if he fails to lead and instruct the whole medical profession in this respect. In private or out-patient practice, and even in ordinary hospitals and sanataria, the results of any mode of treatment are liable to be vitiated by variations of diets and habits of life, which are entirely beyond the ken of the physician. In the hospital for the insane, on the contrary, the diet and habits are under almost absolute control, and observation on the results of treatment should be much more reliable' (4).

Inherent in any research is the uncovering of new and unknown data. Similar to other research activities, therapeutic clinical research

with psychoactive drugs has three distinctly different stages: (1) discovery, i.e. to recognize the psychotropic nature of the drug; (2) verification, i.e. the experimental confirmation of the hypothesis which was elaborated upon uncontrolled observations; and (3) communication, i.e. to convey the information that was obtained (1).

Discovery

The verb discovery means to be the first to find out, see, know about or learn of the existence of something (13). The only basic principle of scientific discovery is an impartial, unbiased and accurate observation in the actual field where the discovery is made. Thus the discovery of psychoactive properties of a drug is a clinical psychiatric discovery; i.e., the discovery of the therapeutic property of chlorpromazine is a clinical discovery which, however, was preceeded by chemical and pharmacological research.

Let us try to see this in an actual example. The chemical discovery of chlorpromazine was made at Rhône-Poulenc-Spécia Laboratories in France (10). It was confirmed and communicated that chlorpromazine is a whitish crystalline powder with a molecular weight of 355.3, a melting point of 195° C, etc. The chemical discovery was followed by the pharmacological discovery. It was revealed and verified that chlorpromazine has antiadrenaline, antiacetylcholine, antihistamine, and anticholinesterase activities, that it facilitates induced hypothermia, reduces oxygen intake, enhances the effect of hypnotics, general anaesthetics, etc. Then, after appropriate toxicity studies on animals and humans, chlorpromazine was given as premedication prior to general anaesthesia. It was a French anaesthesiologist who observed that patients exposed to chlorpromazine premedication became indifferent to the forthcoming operation, and that chlorpromazine premedication prevented postoperative restlessness. Thus the discovery of the psychotropic properties of chlorpromazine was made by the French anaesthesiologist LABORIT (1951) (10), by an unbiased, accurate, *accidental* observation. This was followed by the discovery of the therapeutic potential of the drug in psychiatry by HAMON, PARAIRE and VELLUZ (1952) (7) in which they observed that the drug, in association with pethidine, resulted in transitory sedation in a case of manic agitation, and by the report of DELAY, DENIKER and HARL (1952) (3) who claimed symptomatic control when chlorpromazine was used alone in several cases of manic excitement. While in the discovery of the

psychotropic property of the drug, serendipity played an important role, in the therapeutic discovery, intention was the primary factor.

Nowadays with the development of great numbers of psychotropic drugs with known chemical and pharmacological properties, the majority of therapeutic discoveries are intentional. As a matter of fact, we have reached the point where preliminary pharmacological screening decides whether or not clinical testing is indicated. Since the pharmacological psychotropic parameters were derived primarily from the activity of known psychoactive drugs, this is a real pitfall which may prevent a further breakthrough in drug therapy in psychiatry. One should always keep in mind that: 'a rat is not a man and a healthy animal is not a sick human'. In other terms, besides the similarities, there are also striking differences between the action of drugs on animals of different species including man. In spite of the numerous presently available pharmacological screening techniques for psychotropic drugs, there is still uncertainty regarding how to extrapolate findings from one species to another.

Verification

But since 'one swallow does not make a summer nor one robin a springtime', the observation of HAMON and his collaborators in one single instance, and DELAY and his collaborators on several manic cases, the initial dramatic therapeutic effectiveness of chlorpromazine was not the end but rather the beginning of experiments with the drug. These experiments were intended to verify whether the discovery—the strong therapeutic potential of chlorpromazine in psychiatric cases—could be confirmed or not. Thus, while in the first stage of research, discovery, sound clinical judgement is of the utmost importance, in the stage of verification a sound knowledge of experimental method plays an important role. A lack of experimental sophistication leads to the failure of not providing means, i.e. adequate controls which render the study verifiable.

The experimental method contains four steps: (a) observation; (b) hypothesis; (c) experimentation, (d) induction (6).

Observation and Hypothesis

During the period of observation, the investigator familiarizes himself with the experimental compound. These pilot studies remain uncontrolled and the drug is given in free dosages for different lengths of time to a limited number of patients of different ages, sexes, and

diagnoses with various pathological symptom profiles. In this step great flexibility is required, and rigidity, by limiting the scope of information, is a pitfall. Another pitfall of the observational period is to put in charge of the project a clinically inexperienced investigator who is unable to understand the meaning and significance of what is being observed. This pitfall has serious consequences since these are the observations on the basis of which the experimental hypothesis will be formulated. This hypothesis, when it is first formulated may be indefinite and expressed in very general terms. But this first general hypothesis has to be continually reworked, always more definitely and always more specifically; it has to be broken down into a number of specific unit hypotheses, each of which determines a next experiment which will be carried out independently. In the case of therapeutic clinical testing of psychoactive drugs special emphasis must be placed on formulating the hypothesis, on the criteria of the selection of the experimental population, on the criteria of treatment, i.e. what drug, in what dosage and how long will it be administered; and not the least, on the criteria of how changes towards better or worse will be expressed. If one fails to include any of these criteria in his unit experiment, there is the pitfall of not knowing exactly what one is doing and if we don't know what we are doing, or as WILSON expressed it 'if we don't know what we are talking about we can still talk and most likely talk volubly but there is small chance that we are talking to a definite point' (15).

Experimentation and Induction

After the unit hypotheses have been formulated, we would like to have the answer to our investigation as quickly as possible, using the minimum number of patients for the minimum amount of time, thus obtaining the maximum amount of information from the minimum amount of material. This is fully justified since no one wants to spend more in time and effort than is absolutely necessary, no one wants to withhold a good treatment longer than necessary and no one wants to disseminate dangerous and useless treatments. This goal is achieved by an appropriate experimental design relevant to the nature of the questions (6).

The most crucial questions in the therapeutic clinical testing of psychopharmacological drugs are the following:

(a) Does the compound have any toxic effect if administered in a certain dosage, for a limited period of time to a well defined group of patients?

(b) Does the compound have any therapeutic effect if administered in a certain dosage for a limited period to a well defined group of patients?

(c) Is the compound superior therapeutically to another drug with well-established therapeutic effectiveness in the same area?

This is the point where the problem of controlling the experiment becomes important. Though most investigators agree that in this stage of the experiment a controlled design is essential, many misunderstandings exist, particularly about what a control procedure is. In the therapeutic clinical testing of psychotropic drugs, any procedure or technique that allows one to establish the existence of the phenomenon and its relation to a specific cause—to the drug effect—can be called a control (1). There are different control procedures and which one to choose is always dependent on the nature of the question. In answering the first of the three crucial questions 'Does the compound have any toxic effect if administered in certain dosage for a limited period to a well defined group of patients', we follow either the so-called endogenous control procedure or the exogenous no treatment control procedure. In the first instance each single subject exposed to the treatment serves as his own control while in the second a separate but comparable group of subjects is tested simultaneously with the treated group, but without receiving the medication. If there is any toxic effect indicated in any of the measured areas further decision on the fate of the drug should always depend on the nature and severity of the reaction and on the probability of its occurrence and it should always be balanced with the therapeutic value of the drug. One should never forget that chlorpromazine, the drug which revolutionized psychiatry and brought the most fundamental changes in the therapy and management of the mentally sick, might have been abandoned in clinical usage because of its toxic action on some specific aspect of hepatic function. This toxicity occurs only in a limited number of cases and in most of these cases disappears even as chlorpromazine administration continues. Side effects and adverse reactions with a drug are important findings, while a hasty decision to stop all work with the compound, if they occur, is a pitfall.

In answering the second question, 'Does the compound have any therapeutic effect if administered in a certain dosage for a limited period to a well defined group of patients', we follow the exogenous placebo controlled design with random allotment of patients to the two groups (active compound, placebo). The medical use of placebos—unspecific

stimuli—is not a new invention (11). The therapeutic use of placebo was considered a 'commonplace method' as stated in the Quincy Lexicon in 1787. Then there are only isolated references until in 1945 PEPPER revieved interest in it (12). One year later at the Cornell Conference on Therapy, GOLD (2) gave a new introduction to the use of placebos in therapy and since that time the placebo controlled design in the evaluation of therapeutic efficacy of psychoactive drugs 'burst into methodological and experimental prominence with the explosive brilliance of a supernova' (LEHMANN, 11). While the placebo controlled procedure gives adequate answers to our second question, BIGELOW considers the administration of placebos in the clinical evaluation of psychotropic drugs in a number of instances a source of error. He argues that unless the placebo is administered in such a fashion that an observed emergent can be clearly linked either to the placebo, the test substance, or both, then obviously, administration of the placebo has been fruitless and any consideration of the validity of the given result merely because placebo was given is unwarranted. Moreover, he claims another pitfall arises from the necessity that the placebo itself has to be rigidly controlled. If orally given it must have physical characteristics analogous to the active medication and it has to be administered in the same fashion with identical procedures as the real drug. The same applies if it is injectable (1). In the placebo-controlled design, we use random allotment. This necessitates rather large experimental groups.

In answering the third question whether one or another drug is superior under certain specific conditions, we follow the double-blind controlled procedure with matched-pairs. This makes it possible to derive from relatively small experimental groups valid conclusions. From a theoretical point of view, in human beings where transaction of processes are present, a double-blind controlled study seems to be essential to eliminate the bias that might be introduced through feedback mechanisms between the observed and the observer (11). However, in BATTERMAN and GROSSMAN's experiment the double-blind method for some unknown reason obscured the presence of an actually existing pharmacotherapeutic property of the drug which arose when they switched to a single-blind placebo trial. Furthermore in UHLENHUTH's experiment the therapist's attitude broke through the double-blind experiment and HOFFER and OSMOND (8) argue that the double-blind method, when the group under study is not homogeneous, may obscure the presence of significant differences.

Considering all the pitfalls of the different control procedures the question arises: are control series really essential in therapeutic clinical trials with psychotropic drugs? The answer to this question is yes. They are important since they give a valid estimation of experimental error which is the basis for the statistical tests of significance and because they make the experiment self-contained which enables us to form our conclusions from the experimentally obtained evidence. Finally, control series are necessary since, according to the null hypothesis, our therapeutic results could have occurred by chance. And although by the experimental design in general we try to make such chance events infrequent and as rare as possible, only through a control series can we know what is the frequency or rarity of this chance, the probability that our findings are real (6).

All this points towards the necessity of the application of the statistical method. This is even more underlined if one considers that in every therapeutic clinical trial with psychoactive drugs we are using inductive logic, namely, we consider members of a class and make inferences about the class. The most important kind of induction that we utilize is the statistical kind, i.e., we draw general conclusions on the toxicity, therapeutic activity, etc. of the drug from our limited experimental sample. It is really unfortunate that the statistical method also has its own pitfalls (5). Some of these were expressed by HUNTSMAN by the following: 'the prestige of mathematics is so great that many persons forget that even in mathematical hands, probability, chance and random mean ignorance. They come to think that, in the alembic of mathematics, chance in some way becomes certainty. They take great care to select random samples without realizing that insofar as a sample has been random, they don't know how it was selected' (9). A more severe criticism was launched in the *Lancet* by WIENER quite recently (1962) (14). According to him, many clinical investigators 'because they are unduly sensitive or insecure regarding their lack of mathematic training and knowledge habitually hand over all their data to biometricians for analysis in order that their papers may include the appropriate χ^2 tests, standard errors and so on. In that way they have come to depend more and more on mathematicians who have no knowledge or understanding of the subject to interpret their findings, instead of relying on their own experience and common sense'. WIENER concludes that mathematics is a poor substitute for accurate observations, reliable experimentation, and common sense.

And this leads us to the third and final stage: communication.

Communication

While in the first stage of discovery, clinical experience and judgement and in the second stage of verification, knowledge of experimental design and statistics played prominent roles, communication is again clinically oriented. It should be formulated in simple terms and it should answer the questions the practitioner is interested in: in what conditions, in what dosage, for how long, under what precautions should the new drug be administered. Editorializing and the tendency to present findings not supported by evidence are the common pitfalls (1).

While in the *psychopharmacological era*, the method of therapeutic clinical testing has not really progressed, *the new method, psychopharmacology*, has opened new horizons which we hope will bring in also new methods in therapeutic clinical testing. While the method of drug evaluation has not yet changed, psychiatric patients benefitted more from the new psychotropic drugs than they did from any treatment procedures of the past.

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