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Methodological and Design Issues in Clinical Trials of New Neuroleptics: an Overview

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The recent development of new neuroleptics that differ from the conventional neuroleptics in both mechanism of action and side-effects profile has introduced problems in their clinical assessment, and highlighted ongoing issues in the design and methodology of clinical trials. These issues are broadly grouped and discussed as follows: sampling problems and selection of patients; design issues; problems in measurement; ensuring compliance; recognition of extrapharmacological issues; and statistical models. For patients to benefit from the development of new neuroleptics, clinical settings have to be prepared for testing their efficacy and safety without too much delay in well designed clinical trials.

The dopamine hypothesis was the dominant concept for the pathophysiology of schizophrenia and consequently the model for development of neuroleptics over the past 30 years. All neuroleptics introduced during that period were dopamine antagonists. Like all dopamine antagonists, neuroleptics have a distinct side-effects profile that is easily predicted from their pharmacological actions. Most notable among the side-effects are the extrapyramidal symptoms and the long-term irreversible neurological side-effects. With the expanded knowledge gained over the past few years of the dopamine receptor and its subtypes, and a better appreciation of the role of other receptors in the modulation of dopaminergic functions, a number of new compounds have been proposed as potential neuroleptic candidates. The successful rehabilitation of clozapine and its demonstrated efficacy in chronic schizophrenics resistant to treatment (Kane *et al*, 1988) have also stimulated a search for 'clozapine-like' compounds. Many of the new compounds, at least in animal models, lack the conventional neuroleptic profile in that they lack sedation and have minimal extrapyramidal side-effects. Advances in the development of new therapeutic drugs inevitably introduces a number of problems in the clinical assessment of such new agents. Not only have the new compounds introduced new issues, but also they have highlighted a number of ongoing issues that frequently confound the design of clinical trials and the interpretation of results. This paper selectively deals with a number of these issues.

Sampling problems and selection of patients

Approach to diagnosis

Over the past two decades, various definitions of psychiatric syndromes have come into widespread use not only for research purposes but also for everyday clinical practice. For schizophrenia, there is a multiplicity of diagnostic systems that have been employed in various clinical trials. Though one expects valid and reliable diagnostic systems to give similarly concordant results, such is not frequently the case among a number of existing diagnostic systems in schizophrenia. In the course of a prospective study, my colleagues and I examined the contribution of various diagnostic criteria in predicting response to neuroleptics (Awad & Hogan, 1988). Classifying our sample of 55 chronic schizophrenics in acute relapse according to three diagnostic systems, we arrived at three different conclusions. According to the Feighner criteria (Feighner *et al*, 1972), our sample included 25 instances of 'definite' schizophrenia and 8 of 'probable' schizophrenia; 22 patients were classified as 'undiagnosed'. Applying the Research Diagnostic Criteria (Spitzer *et al*, 1985) gave diagnoses of schizophrenia narrow for 36 patients, schizophrenia broad for 15 patients, and other for 4 patients. Using World Health Organization flexible criteria (Carpenter *et al*, 1973), 23 patients met at least five criteria and 32 patients met six or more criteria. Thus, employing three commonly used diagnostic systems for schizophrenia, different conclusions about diagnosis can be drawn out. This discordance in diagnosis not only can alter results of clinical trials, but also makes comparisons between studies almost meaningless.

In the light of this state, the comments of Helzer & Coryell (1983) about lack of consistency of findings in biological psychiatric research are not surprising: ". . . it is frustrating to think that differences in results across studies may still be partly attributed to criterion variance".

Homogeneity concerning previous response to neuroleptics

Schizophrenia is a heterogeneous disorder with regard to aetiology, pathophysiology and consequently treatment outcome. It is clear that not all schizophrenics benefit equally from medication and some patients may not derive any benefit from it at all (Leff & Wing, 1971; Prien *et al*, 1977; Davis *et al*, 1980). In addition, it has been questioned whether a subgroup of schizophrenics not only may fail to derive any benefits from neuroleptic therapy but even may deteriorate in some aspects of their functioning (Judd *et al*, 1973; Hogarty *et al*, 1974; Rappaport *et al*, 1978). Unless one controls for this important confounder in the assessment of new neuroleptics, it is conceivable that some treatment-resistant subjects cluster in one or another of the treatment groups, skewing results. Thus, unless subjects enrolled in a study generally belong to the same prognostic range as far as their previous responsiveness to neuroleptics is concerned, attempts to relate outcome to drug-therapy variables may fail.

Similarly, as heterogeneity exists, one would expect that certain clusters of symptoms or subgroups of the disorder might respond differentially to different neuroleptics. The conclusion at present is that there seems to be no good evidence for differential effects of various available neuroleptics related to subtypes of schizophrenia (Awad, 1989). However, the issue may have been obscured by methodological limitations. It is possible that designs which compare pharmacological treatment methods using group means may be incapable of detecting the responses of smaller homogeneous subgroups that are generally buried in the group means (Wolkowitz *et al*, 1990).

Sample size and problems of recruitment

Anyone who has been involved in clinical trials of neuroleptics on schizophrenics recognises the difficulties in recruitment. In the acute phase, patients are frequently disturbed, with the result that it is impossible to randomise them to an experimental drug or placebo, not to mention the difficulties of getting informed consent. Such common restrictions introduce problems in that those who are likely to be included in clinical trials are patients whose illness is generally mild to moderately severe, or those chronic patients who frequently are less sensitive to neuroleptic effects. This introduces bias in that the study population is chosen from potentially one tail of the distribution.

Ensuring adequate sample size continues to be a major problem in clinical trials of neuroleptics. To overcome such problems, multicentre clinical trials have become a standard practice. An increase in sample size can increase the power of the findings. However, it can also increase potential bias. Individual differences among physicians in their clinical approaches and differences between clinical settings in their orientation and approach to treatment are only a few of the potential biases in multicentre clinical trials. In addition, increasing the size of the sample does not necessarily resolve problems of reliability of diagnosis or measurement. Recent guidelines established by the working parties on multicentre clinical trials of the Council of the International Federation of Associations of Pharmaceutical Physicians deal with a number of these critical issues and make useful recommendations for the conduct of multicentre randomised clinical trials (Lucchelli *et al*, 1990).

In the past few years, with the development of a large number of potential neuroleptics that require clinical assessment, many clinical settings involved in clinical trials find themselves overcommitted. As the process of clinical assessment of neuroleptics is slowed down, pressures have mounted to involve as many centres as possible. This unfortunately has led to too few patients enrolled from too many centres. There has to be a minimum optimum number from every centre to ensure quality and improve the analysis of results.

It is worth exploring why a large sample size is needed. Frequently the design includes too many variables that will require a large sample size. Altering the experimental condition in a clinical trial to achieve larger differences between treatment groups is preferable to trying to make a small difference statistically significant by employing a very large sample size.

Sex difference in drug response

Sex difference in response to neuroleptics has not received adequate attention, in spite of results of early clinical trials that reported larger drug/placebo difference in females than in males (Goldberg *et al*, 1966). Several studies have shown that women seem to require lower doses of neuroleptics (Seeman, 1983). Recently, it has also been reported that males may have more negative symptoms (Gaebel, 1989), an important issue that may influence the outcome of drug therapy, since such negative symptoms are less sensitive than positive symptoms to neuroleptic effects.

Design issues

Use of placebo or a standard neuroleptic as a control

One of the main objectives of controlled clinical trials for new neuroleptics is to demonstrate efficacy. This can be achieved by demonstrating either that the new drug is more effective than placebo or that it is equally effective as a standard neuroleptic. The inclusion of placebo groups frequently provokes practical and ethical problems, particularly in clinical trials on acutely psychotic patients. The questions frequently raised are: Do we need a placebo group to demonstrate efficacy? Can alternative designs that demonstrate dose response eliminate the need for placebo groups?

My colleagues and I recently completed a multicentre clinical trial with the new selective dopamine D_2 neuroleptic, remoxipride, in acutely psychotic schizophrenics (Lapierre *et al*, 1992). The design was dose-ranging, including three groups treated with different dose ranges of remoxipride and a control group treated with the standard neuroleptic, haloperidol. To demonstrate a statistically significant difference between treatment groups, our design required 60 patients per group, which made the study quite lengthy and expensive and required the involvement of at least ten centres. With excellent coordination and quality control, the study yielded valuable information, in that the lower remoxipride dose range 30–90 mg per day proved to be not as effective as the intermediate (120–240 mg) or the high dose range (300–600 mg). Thus, the low dose range behaved in some way as placebo. The responses of the intermediate and high remoxipride dose range groups were comparable with that of the haloperidol-treated group. In this design, all patients were treated with active drugs. The results also provided valuable information establishing effective dose ranges for the new neuroleptics in the treatment of acute psychotic episodes. On the other hand a design comparing two groups treated with remoxipride and placebo would have required far fewer subjects.

An alternative compromise design was employed recently by Manchanda & Hirsch (1986), in their study of possible antipsychotic effects of propranalol. In their design, all patients received for the first week haloperidol as well as either the experimental drug (propranalol) or placebo on a randomised basis. Starting the second week, haloperidol was withdrawn and both groups continued on their assigned drugs. Thus, all acutely psychotic recently admitted patients were treated with a neuroleptic for the first week, which satisfied ethical expectations and to some degree stabilised the patients to allow their continued participation in the study.

Different side-effects profile of the new neuroleptics

Many of the new neuroleptics lack sedative effects. Remoxipride, as an example of the new selective dopamine D_2 antagonists, lacks sedation. In our multicentre study comparing remoxipride with haloperidol, 35% of patients on remoxipride required at some point a sedative as compared with 19% on haloperidol. Not recognising this issue in design might have led to more patients in the experimental group being taken off the clinical trial because of lack of sedation.

Another design problem is the reduction in extrapyramidal symptoms, which can undermine the issue of blindness. Kane *et al* (1988), aware of such potential bias in their design of the clozapine study, included an anti-Parkinsonian routinely in their haloperidol groups, and obviously had to match it with a placebo in the clozapine patients. Although this approach complicates the design, as it adds one more drug or placebo, without it the issue of blindness is in question. In addition, the extrapyramidal side-effects in the haloperidol group might have undermined the proper assessment of clozapine efficacy.

Dose equivalency

Existing guidelines of equivalency among neuroleptics are frequently neither practical nor accurate. Tables of suggested dose equivalence have been described as crude and of questionable validity (Kane, 1989). This can be a source of bias in that patients can be undertreated with an experimental drug or a standard that makes it possible to conclude that the drug is less efficacious. Similarly, choosing a much higher dose of the standard can lead to more side-effects, with the conclusion that the experimental group has fewer side-effects.

Short-term or long-term designs

The average length of a clinical trial on acutely psychotic patients usually is 4–6 weeks. Although these acute studies are necessary as an initial step, frequently they do not yield enough information about how the experimental drugs would fare in long-term use. In addition, the sample used in acute studies represents only a portion of the population in a particular phase of the illness, which is a frequent source of bias in clinical research. Clinical trials on chronic schizophrenics pose problems of different kinds, as many of these patients have been on neuroleptics for a long period. The notion of

withdrawing them from neuroleptics or randomising them to treatment groups is frequently met with reluctance of the clinical staff because of a real fear of destabilising the patients' condition. Another problem with such patients is that frequently they are on more than one neuroleptic and probably other psychoactive drugs. It is important in this population to include the use of a rescue drug in situations of impending relapse. This approach requires clear definitions of symptoms of impending relapse. The choice and frequency of use of rescue drugs can be problematical. Can the rescue drug be a benzodiazepine or another neuroleptic? The use of another neuroleptic frequently confounds the statistical analysis of results. A better alternative is that the design allows for flexible dosing. This allows the investigator to increase the dose of the experimental drug or the standard to avert relapse. However, this approach will not prove adequate in the case of patients on placebo. This perennial issue as well as other issues has stimulated designers of clinical trials as well as investigators to look for alternative designs.

Alternative designs

One of the innovative new designs is the survival-analysis study. All patients are treated first in the conventional way, then randomised to experimental drug or placebo. The end-point then is the time between entering the study and first relapse. Such a design may yield valuable information about the ability of the experimental drug to prevent relapse, but at the same time poses a number of practical problems. A clear definition of 'relapse' is required. Another problem is how to deal with short-term relapse, where the patient shows some signs of relapse but recovers quickly. This has led to another innovative approach, utilising 'well time' rather than 'time to relapse': one considers the entire time the patients were well and not psychotic. Though these approaches may provide valuable information that is not easily obtained in short-term studies, they create several serious problems, particularly in the statistical analysis, since follow-up times can be extremely variable. They require the close involvement and expertise of the biostatistician.

Problems in measurement

Appropriateness of scales used for measurement

Although the reliability of scales used for measurement can be improved by the training of observers and clarification of definitions, there is no way to compensate for low validity (Kraemer *et al*, 1987). One of the serious problems in psychiatric research is demonstrating the validity of the measurements we use (Snaith, 1991). Many scales are simply groups of items believed to be related to some underlying trait or state, but not necessarily demonstrated to be so related. For example, in assessing negative symptoms in schizophrenia, scales include items such as affective flattening, alogia, apathy, anhedonia and asociality or attention problems. The range of negative symptoms used is wide (deLeon *et al*, 1989). Although the correlation between total scale scores is fair, agreement on the presence or absence of syndromes is weak (Fenton & McGlashan, 1992).

In addition to the need for validity of criteria, there is a need for objectifying our clinical observations. Several investigators achieve objectivity in their measurements using approaches such as blind assessments of samples of voice (Kruger, 1989), or measuring video-taped affective response of patients to an experimental situation (Ellgring, 1989). However, such approaches require some technical capabilities which are frequently not practical for many of the clinical settings.

Definition of response or lack of response

Different studies have employed different definitions for response. Some studies have used change of at least 50% in total baseline score in symptoms, whereas other studies have used a much smaller improvement. It is preferable to use a composite definition of response across a number of parameters that are sensitive to drug effects, rather than relying completely on one parameter as symptom change. The definition of response or lack of response has to be established clearly in advance. Such a definition has to be established in the context of the population studied. A small change in a chronic or treatment-resistant population may make a lot of difference, but it may not be enough in an acutely psychotic population.

The issue of quality of life on neuroleptics

Anyone who has not been closely involved with clinical trials of neuroleptics in the last 20 years may have thought that questions related to quality of life on neuroleptics have always been an important objective of assessing new neuroleptics. Unfortunately, that is not so. Even in the few clinical trials with neuroleptics that reported some evaluation of aspects of quality of life, such measures in most of these trials were thought up after the design had been implemented rather than as one of the primary objectives. Several reasons have been raised as an

excuse for not including such an important dimension in clinical trials (Awad, 1992): (a) lack of agreement on the definition of quality of life; (b) doubt concerning the reliability of information from schizophrenic patients about their feelings or satisfaction; and (c) lack of a conceptual model for quality of life on neuroleptics.

Although there may be a lack of agreement on what is 'quality of life', operational definitions exist. Furthermore, such an approach has been extensively used in chronic medical illness such as arthritis or cancer. Although schizophrenic patients frequently experience disturbed thinking and communication, recent medical and nursing literature, including that from my group, suggests that the feelings and attitudes of schizophrenic patients towards their treatment can be elicited, and that satisfaction in their life is not only possible but also important (Hogan *et al*, 1983; Davidhizar, 1985). Recently, an integrative model for quality of life on neuroleptics was proposed (Awad, 1992). According to this model, the major determinants of quality of life on neuroleptics are schizophrenic symptoms and their severity, side-effects profile and psychosocial performance. Anyone of these factors has to be taken not only as a significant component but also as a likely determinant of treatment outcome, and consequently of quality of life. Symptom change and side-effects are already measured in clinical trials. What is needed is to add the dimension of functional performance. After all, the ultimate in any drug therapy is how patients feel and function on the medication.

Ensuring compliance

There is agreement among clinicians and researchers that the level of non-compliance of patients concerning prescribed medication can be as high as 30–50% (Blackwell, 1982). With more reliance on out-patient clinical trials, compliance becomes a critical concern. The problem with compliance is the lack of satisfactory objective measures. The most obvious means of documentation such as pill count, or blood or urinary screening have not proved adequate (Sacket & Haynes, 1976). Many of these spot-checks pertain only to a limited time period and do not indicate what is happening between visits. Obviously, efficacy or lack of efficacy cannot be demonstrated unless medication is taken. Recently, an electronic monitoring device has been developed that allows medication to be dispensed in a container having a special electronic cap that records the time and date of each opening of the container (Kramer *et al*, 1989). The recorded pattern of these openings provides presumptive measurements of the patient's dosing history for each day of the entire time since the previous visit. Obviously, electronic monitoring is not foolproof, as the container could be opened without any medication being ingested. Unlike someone who discards pills before a periodic pill count, a person who wanted to fool the monitoring circuit would have to trigger it according to the appropriate schedule each day, a task to which most patients would be no more likely to adhere than that of actually ingesting their medication. This device has been extensively used and reported on in internal medicine and paediatrics literature, but unfortunately it has not yet been applied widely to psychiatric populations. Unfortunately, the device is still relatively expensive; however, if one can ensure compliance then the investment is worthwhile in order to ensure the quality of already expensive clinical trials.

Recognition of extrapharmacological issues

Quality of therapeutic relationship and context of treatment

It is recognised that such phenomena as the characteristics of the setting where treatment takes place or the quality of the doctor–patient relationship have an impact on the outcome of therapy. Sarwer-Foner (1963) has argued that ". . . drug response needs to be understood in terms of the context in which it is given as well as the patients' and doctors' conscious and unconscious expectations and fears". These issues are particularly relevant in clinical trials with multiple investigators or multiple centres. However, they are rarely controlled for, nor is it possible frequently to control for their effects on outcome. Another important issue which frequently receives little attention is how much concomitant therapies, whether psychotherapy or occupational therapy, may influence outcome in clinical trials, and if it is possible at all to quantify their impact.

Subject's feelings on neuroleptics and their relevance to compliance and outcome

Many reports have already linked negative response of subjects on neuroleptics to compliance and outcome (Van Putten & May, 1978; Van Putten *et al*, 1981; Awad & Hogan, 1985). The concept of subjective response to neuroleptics, and its validity and measurement have been described in detail previously (Hogan *et al*, 1983; Hogan & Awad, 1992). It is possible that patients who tend to have less favourable outcome to drug therapy and non-compliant patients are one and the same, and are characterised by their negative subjective responses

to neuroleptics. This raises the question of whether it is important in clinical trials of new neuroleptics to evaluate how patients subjectively feel on the medication, since that may be a factor in their eventual compliance, and ultimately related to outcome.

Statistical models

Overinclusiveness in outcome measures and data collection

The accessibility and ease of use of computers have made it possible to access complex statistical procedures in spite of the little knowledge that investigators have about such complex analytical approaches (Kramer *et al*, 1989). This carries the danger of misinterpreting data. Similarly, there is always temptation to collect more data than needed, and to add more measures, since computers have a tremendous capacity to handle excessive amounts of information. In the end, overinclusiveness of data can lead to redundancy and lack of clarity of final conclusions.

Bring in the biostatistician early on the design

It is essential to involve the biostatistician from the initial phase of designing a study through data-gathering and final analysis. The complexity of clinical trials, as well as their cost, is increasing. With early involvement, a biostatistician can help to avoid serious pitfalls in design and maximise the utility of data collected from clinical trials, as well as helping in the preparation of the final report.

Conclusions

An exciting era in the development of new neuroleptics has started. For patients to benefit from such accelerated development, clinical settings have to be prepared for the challenge of testing the efficacy and safety of new neuroleptics. For that, a number of 'old issues' as well as a number of 'new issues' brought about by the different profiles of the new compounds require serious attention in the design of clinical trials so as to expedite the process. Obviously, a number of issues will linger with us, as at present there may be no adequate resolution to some of them. However, the realisation and recognition of the existence of such confounding factors is important for the proper interpretation of data. Based on the literature and the experience of my group, the following recommendations can be made.

Recommendations

(a) Ensure diagnostic consistency, employing standardised commonly used diagnostic criteria.

(b) In clinical trials of *new* neuroleptics, it is necessary to ascertain history of previous response to neuroleptics as well as including patients previously responsive to neuroleptics.

(c) Limiting the variables and maximising the difference between treatment groups can reduce the need for a large sample size.

(d) Sex difference in drug response ought to be recognised in study design.

(e) Whenever placebo-controlled studies are not feasible, alternative designs are available and already tested.

(f) In double-blind evaluation of new neuroleptics against standard neuroleptics, blindness has to be ensured in view of different side-effects profiles.

(g) Functional status and quality of life on neuroleptics ought to be included as an outcome measure.

(h) Consult with the biostatistician early in the design and choose the appropriate statistical model.

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