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Clinical Trials

Influence of Selection of Patients on Results of Clinical Trials

J. P. LEFF

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Summary

The hypothesis is advanced that any population of patients can be divided into those with a good prognosis, a poor prognosis, and an intermediate prognosis in respect to a particular treatment. The outcome of a clinical trial of treatment will be partly determined by the proportion of patients selected for the trial from each of these prognostic groups. The implications of the hypothesis are illustrated by consideration of three recent trials of treatment for psychiatric patients.

Introduction

Let us consider a population of patients suffering from a specific condition who are to be exposed to a particular treatment for the first time. A treatment is rarely found which is completely effective for every sufferer from a particular disease. There is usually a substantial proportion of patients who fail to respond to the treatment, though suffering from the same condition as others for whom the treatment is effective. There is also likely to be a group of patients whose constitution enables them to overcome the illness without any treatment. The administration of treatment to this group would not alter the course of the illness at all. It is convenient to label the patients who would recover without treatment those with a "good prognosis," and the patients who fail to respond to treatment those with a 'poor' prognosis." The remainder, whose illness is affected beneficially by treatment, will be referred to as those with an "intermediate prognosis."

What is the effect of entering this total population of patients, with a whole range of prognoses, in a clinical trial of active treatment versus placebo? If the standard procedure of random assignment of patients to each treatment condition is used then both the active treatment and placebo groups will contain the same proportions of patients with a good, a poor, and an intermediate prognosis. The patients with a good prognosis will recover whether they receive active treatment or placebo, whereas the patients with a poor prognosis will fail to recover whether or not they receive active treatment. Hence, among these two groups of patients with a good and poor prognosis there will be no difference in recovery rate between those on active treatment and those on placebo. It is only among the group of patients with an intermediate prognosis that any difference in recovery rate will appear between those on active treatment and those on placebo. This advantage of active treatment over placebo could easily fail to reach statistical significance if sufficient proportions of patients with a good and a poor prognosis were included in the trial. The lack of a difference between active treatment and placebo among these two groups could conceivably swamp the difference appearing among patients with an intermediate prognosis. Hence the selection of patients with varying prognoses for a clinical trial may influence the outcome. This hypothesis is illustrated by the methodology and results of three recent trials of treatment for psychiatric patients.

Medical Research Council Social Psychiatry Unit, Institute of Psychiatry, London SE5 8AF
J. P. LEFF, M.D., M.R.C.PSYCH., Research Worker

Present Study

TRIAL 1

The first trial[1] concerned the effectiveness of chlorpromazine and trifluoperazine as maintenance therapy for acute schizophrenics. A standard double-blind, placebo-controlled design was used. Of the patients judged on clinical grounds to be suitable for the trial only a small proportion (30%) actually entered the trial. Of those who did not enter the trial, for which there was a variety of reasons, two groups of patients were excluded by the consultants concerned. One group was thought to be too precarious to risk the possibility of having the active medication replaced by a placebo. The other group was thought to be well enough not to need maintenance treatment. All patients assessed as potentially suitable for the trial were fol-

lowed up, whether or not they actually entered the trial. This enabled an assessment to be made of the prognosis given by the consultants to these two groups of excluded patients.

The follow-up of the trial patients showed that active drug was significantly more effective as maintenance therapy than placebo. The follow-up of the excluded patients proved that the consultants' prognostications were substantially correct. The patients ascribed a good prognosis and not maintained on any treatment had a low relapse rate. The patients ascribed a poor prognosis had a high relapse rate despite being maintained on treatment. In fact their relapse rate (66%) was identical to that of a group of patients who declined to attend outpatients and did not take any maintenance treatment. It appears that the consultants quite knowingly entered in the trial only those patients with an intermediate prognosis, in whom the effectiveness of maintenance therapy was clearly seen. There was no evidence, however, that maintenance therapy was of any benefit to the bulk of patients who were excluded from the trial.

TRIAL 2

The second trial[2] concerned the effectiveness of maintenance therapy with long-acting injections of fluphenazine decanoate for chronic schizophrenics. A high proportion (86%) of the patients in this trial were selected from the clientele of an established fluphenazine clinic. Most patients in the trial (69%) had been on fluphenazine injections for over a year and only 5% had been receiving them for less than a month. Patients with a good prognosis are unlikely to be started on fluphenazine injections, which are often reserved for patients with many relapses or for those who are thought in need of maintenance treatment but who refuse to take tablets. In an established clinic in which a particular treatment is being prescribed the doctors tend to experiment with the dosage, lowering it gradually and watching for the return of symptoms. Those patients with a good prognosis who are prescribed fluphenazine injections will remain free of symptoms even when the treatment is discontinued, and are likely to be discharged from attendance. Patients with a poor prognosis will relapse despite maintenance therapy and will mostly be changed to some other form of treatment after several relapses. Hence, over a period of time patients with a good prognosis and those with a poor prognosis will be taken off the treatment, so that the bulk of those remaining on treatment, assuming that it is effective, will be those with an intermediate prognosis. A placebo-controlled trial of treatment in this intermediate group is more likely to show a clear advantage of active treatment over placebo than if the other two groups were also included.

In the event, in the fluphenazine trial there was a dramatic difference between the two groups—only 8% of patients on active injections relapsing compared with 66% of those on placebo. Unfortunately information was not available concerning any patients who might have been excluded from the fluphenazine clinic because they either did well without the injections or relapsed despite them. Hence the trial sample cannot be related to the wider population of chronic schizophrenics as was possible with acute schizophrenics in the trial of Leff and Wing.[1]

TRIAL 3

The third study[3 4] was a trial of continuation therapy with tricyclicantidepressants for depressed patients. This was organized on a multicentre basis and also used a double-blind, placebo-controlled design. Both amitriptyline and imipramine were tested against a placebo. The patients receiving continuation therapy with amitriptyline had a significantly lower relapse rate than those on the corresponding placebo, but the same advantage was not found for imipramine. In all, 34 psychiatrists from the various centres entered patients in the trial, but the patients were distributed unevenly among these psychiatrists. The 17 psychiatrists from London contributed 36 patients, the three psychiatrists from Glasgow 31, and the 14 psychiatrists from all other centres entered 25 patients. It is evident that the Glasgow psychiatrists individually entered far more patients than the psychiatrists from the other centres. In fact, nearly all the Glasgow patients were contributed by one psychiatrist. If we examine the results in the Glasgow patients separately from the other centres' patients some interesting differences emerge.

Relapse Rates in Various Sub-groups of Patients (Adapted from Mindham et al. [4])

	Active		Placebo		Significance
	No. of Subjects	Relapsed No. (%)	No. of Subjects	Relapsed No. (%)	(Fisher's Exact Test)
London ..	21	4 (19)	15	8 (53)	0·04
Glasgow ..	16	3 (19)	15	4 (27)	Not significant
Elsewhere ..	13	4 (31)	12	9 (75)	0·03

Among the Glasgow patients the relapse rates of those on active drug and placebo are almost identical, and the significant advantage of active drug over placebo shown by the patients from other centres does not appear among the Glasgow patients. The possible reason for this may be found by comparing relapse rates in drug and placebo groups separately. This is not a usual statistical procedure but is justified by the following argument.

Outcome of Hypothetical Groups

Group	Active	Placebo
Good Prognosis	+	+
Intermediate Prognosis	+	−
Poor Prognosis	−	−

+ good outcome, − poor outcome.

Let us assume that the outcome of two samples of patients is being compared. The first group consists predominantly of intermediate prognosis patients. If the second group consists predominantly of good prognosis patients then it is evident from the figure that a difference in outcome will appear only among the patients on placebo. Conversely if the second group consists predominantly of poor prognosis patients then a difference in outcome will appear only among the patients on active drug.

The relapse rate of the Glasgow patients on active drug is not higher than that of patients from other centres. Hence, we can conclude that the Glasgow sample did not include subjects with a particularly poor prognosis. On the other hand, the relapse rate of the Glasgow patients on placebo is *significantly* lower than the corresponding rate for all other centres ($P=0·02$). This strongly suggests that the Glasgow psychiatrists were including in the trial a wider selection of patients than the other psychiatrists involved, and that their selection procedure was biased towards patients with a good prognosis. This was confirmed by personal communication by the Glasgow psychiatrist who contributed the greatest number (29) of patients. He stated that the psychiatrists in his centre made great efforts to obtain patients in view of the small numbers entering the trial in the other centres. In particular, he "wrote to general practitioners who regularly referred their cases here, asking them to send their depressed patients to the clinic before prescribing any medication."

It is reasonable to suppose that the patients referred in response to this plea would be less seriously depressed than those usually seen as outpatients, and that a substantial proportion of them would have recovered from their depression without treatment. Possibly these patients biased the Glasgow sample in the direction of a good prognosis, and hence obscured the effectiveness of the continuation therapy. We can assume

from the few patients contributed that the psychiatrists in the other centres were far more selective and entered only those they judged to have an intermediate prognosis.

Conclusion

The hypothesis put forward derives reasonable support from the first and third studies considered, but its application to the fluphenazine trial is purely speculative. It does, however, provide an explanation for conflicting results from trials of the same treatment. It also suggests that positive results of clinical trials are unlikely to be applicable to the whole range of patients suffering from a particular condition.

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Medicine in Old Age

Diet in the Elderly

D. CORLESS

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The King Edward's Hospital Fund's 1965 report of an investigation into the dietary of elderly women living alone starts by stating "The precise nutritional needs of old people are unknown." Such is still the case today. Logically the subject may be divided into two headings: (1) overnutrition, and (2) undernutrition, with malnutrition affecting both groups. Nevertheless, though Sheldon noted that 20% of women over 80 were overweight, overnutrition can hardly be said to be a major problem in clinical geriatrics, even though it may produce sequelae such as atheromatous degeneration and osteoarthrosis.

The precise definition of both undernutrition and malnutrition becomes impossible if the normal nutritional needs are not known. Opinions vary widely about the incidence of malnutrition, particularly if subclinical malnutrition is looked for. Not surprisingly the incidence depends on the type of person investigated; thus it is lower in incidence among healthy people living at home than in enfeebled people in institutions. Geography has some bearing by reason of social factors, and the amount of sunlight and racial factors may also influence the incidence. Practising geriatrics in a predominantly working class area with a low retirement income, I find malnutrition in one form or another to be very common in hospital admissions.

Social, Clinical, and Environmental Factors

To consider diet in isolation could become an intellectual abstraction, for eating is not solely to sustain life: the preparation and consumption of food is done with others for enjoyment. Thus social isolation due to bereavement or families living some distance away plays a large part in malnutrition. Furthermore, depression in all its shades may be responsible for much self-neglect, while increasing physical infirmity leads to problems in shopping and cooking, compounded by poor housing and the isolation of houses from shops. Retirement to a "place near the sea" often brings unexpected difficulties when infirmities develop.

Illness in old age may lead to an inadequate diet, and it is important to remember that diseases of the gastrointestinal tract complicated by malabsorption may be asymptomatic. Very often the patient forgets to say that he has undergone a gastrectomy. Jejunal diverticula may be found in patients with osteomalacia or vitamin B_{12} or folic acid deficiency. Idiopathic steatorrhoea can present in the elderly and blind-loop syndromes may also be seen. Drugs present an additional nutritional hazard and it is well known that barbiturates and anticonvulsants lead to folic acid deficiency. Not so widely recognized is that these drugs may precipitate osteomalacia because of an increased rate of breakdown of vitamin D metabolites.

Long-stay patients in institutions are often bereft of sunlight and have diets low in vitamin D and sometimes calcium. Thus, not surprisingly institutional osteomalacia may occur as well as scurvy, iron deficiency, and folate deficiency: 20% of patients recently admitted to hospital from a chronic sick institution were found to have biochemical osteomalacia.

The Ideal Diet

Longitudinal studies of the diet of old people show that there is an élite group whose nutrient intake is high and changes little with age. In others the nutrient intake declines probably owing to illnesses. The oft quoted "normal" decline in dietary intake after 80 is probably due to cross-sectional studies being used.

The total calorie intake needs to be related to energy expenditure, which is often quite low—even below 2,000 calories. Thus a reducing diet often has to be much lower than realized—600-800 calories, for instance.

The élite group referred to above was notable for having a high protein intake, 70 or more g per day; 58 or 60 g is the estimated need.

To provide 30% of the required number of calories would mean a fat content of 66 g for a 2,000 calorie diet and hence the normal intake of fat could vary from 50 to over 100 g.

Sixty per cent. of the calorie requirements can be derived from carbohydrates, 266 g being needed for a 2,000 calorie diet.

The estimated vitamin needs are shown in table I.

Department of Geriatric Medicine, St. Bartholomew's Hospital, London EC1
D. CORLESS, M.B., M.R.C.P., Consultant Geriatrician