PAPERS AND ORIGINALS

Trial of Maintenance Therapy in Schizophrenia*

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Summary

A double-blind, placebo-controlled trial was carried out to determine the value of maintenance therapy with phenothiazines in a population of outpatients who had recently recovered from an acute episode of schizophrenia. The drug was shown to be significantly more effective than the placebo in preventing relapse. The relationship of the trial patients to the population from which they were selected was defined in terms of clinical, historical, and social data. Maintenance therapy seems of little value in patients with a good prognosis and in the severely ill, but it is of value in the indeterminate group between these two extremes.

Introduction

The effectiveness of the phenothiazine drugs in the treatment of acute episodes of schizophrenia is now well established (Rathod and Rees, 1958; Cole, 1964), but their prophylactic use in the patient who is free of symptoms or at a steady level of symptomatology rests on much less solid evidence. Numerous studies purport to explore this aspect of treatment but because of defects in design and execution no definite conclusion can be drawn. One of the central problems is the definition of schizophrenia. The criteria for making such a diagnosis are very rarely stipulated in these papers (Engelhardt *et al.*, 1963), but it is well known that considerable differences exist between psychiatrists in their use of diagnostic labels. These differences are particularly pronounced between American and British psychiatrists. Kendell *et al.* (1971) showed that psychiatrists in New York hospitals diagnose schizophrenia in almost twice as many patients as psychiatrists in London hospitals.

American psychiatrists' concept of schizophrenia includes all of what British psychiatrists would call schizophrenia, almost all that they would call mania, and a considerable proportion of what they would call psychotic depression, personality disorder, and neurosis. This all-inclusiveness renders difficult any comparison between American and British studies on schizophrenia. This is particularly relevant as there is no study of British schizophrenic patients which evaluates the effectiveness of maintenance phenothiazine treatment in an outpatient setting. In view of the differing diagnostic habits discussed above it is necessary to stipulate the diagnostic criteria used in selecting patients for any future study.

Most research workers in the field of clinical trials are aware that an initially large population of apparently suitable patients often seems to shrink to a small fraction when attempts are made to apply experimental procedures. The end result is a group of highly selected patients which is very unlikely to be representative of the population from which it is drawn. Ideally, patients who are apparently suitable on grounds of diagnosis and other clinical criteria but who for various reasons have to be excluded from the trial should have their relevant characteristics documented in order to allow comparison with the experimental group. This is particularly important in a therapeutic trial, from which generalizations about the treatment of a particular illness are likely to be made. Almost none of the studies reviewed included information about the population from which the experimental subjects were selected, and none was able to specify the characteristics of non-trial patients or even how many of these there were.

The degree of chronicity of schizophrenia may be an important variable in determining the response to maintenance treatment, as schizophrenia is considered by some to be a progressive disease and it is conceivable that treatment might be effective in the early stages of the illness but not later on. All the studies reviewed have concentrated on the chronic schizophrenic patient but a few have also included patients with a short duration of illness.

Reported Studies

Another important variable is whether the study is carried out on patients in hospital or in an outpatient setting. Patients in

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the protective environment of a hospital are shielded from many of the stresses experienced by patients in the community which might lead to relapse. Most of the studies of discontinuation of maintenance therapy have been carried out on inpatients (Good *et al.*, 1958; Shawver *et al.*, 1959; Diamond and Marks, 1960). Very few have been carried out on patients in the community, and even fewer have used a double-blind, placebo-controlled method. Only the study by Pasamanick *et al.* (1964) and the series of studies by Engelhardt *et al.* (1960, 1963, 1964) and Engelhardt and Freedman (1970) meet these criteria. Unfortunately these studies have a complicated design which clouds interpretation of the results. Both groups of workers entered patients into their trials while they were suffering from florid symptoms of schizophrenia. The patients were placed on drug or placebo and were then followed up for over a year. Thus the studies were initially comparing the relative effectiveness of drug and placebo in controlling the acute symptoms of schizophrenia. It is only later on in the course of these trials that the maintenance effect of the drug was being tested, and by that time the patients whose acute symptoms could not be controlled by placebo had already been withdrawn. The efficacy of preventive medication is not tested in this group. It is possible that they would benefit more from maintenance therapy with an active drug than those who weather an acute episode of schizophrenia while on a placebo. Hence the design of these trials may include a considerable bias.

The study by Gross (1960) is more comparable with the present work but suffers from various weaknesses. He randomly assigned a group of 144 outpatients to either drug or placebo treatment. Double-blind precautions were not observed. Not all the patients were given a diagnosis of schizophrenia, and the criteria for making this diagnosis are not stated. The criteria for relapse were unusually wide and included progressive increase in the severity of neurotic symptoms and the development of persistent insomnia, anxiety, or tension of a severe degree. Most patients were chronically ill, with a total length of previous hospitalization of over one year. However, 25 patients had experienced less than six months' previous hospitalization. The relapse rate of patients on placebo was significantly higher than that of the drug patients.

One further point merits consideration and that is the unreliability of outpatients in taking their medication. Wilcox *et al.* (1965) showed that about half of all outpatients on chlorpromazine failed to take their medication as judged by urine tests. A similar result was obtained by Parkes *et al.* (1962) from careful inquiry of schizophrenic outpatients. This unreliability is by no means confined to psychiatric patients, but is found to a similar extent in epileptic outpatients (Gibberd *et al.*, 1970), outpatients prescribed para-aminosalicylic acid (Luntz and Austin, 1960), and pregnant women prescribed oral iron (Porter, 1969). A variety of measures are available for checking on reliability in drug taking. These include counting returned tablets, urine tests, and simply asking the patient directly. Even when one knows for sure that the patients are taking their medication, surprisingly large differences are found in serum levels of drugs such as nortriptyline, where the variation may be tenfold (Åsberg *et al.*, 1970), and chlorpromazine, where it may be threefold (Curry *et al.*, 1970). At the moment there is no way of controlling for such variations in serum level, but this factor should be considered when interpreting the results of drug trials.

Method

The present trial was designed to take into account the considerations discussed above. The main aim was to discover whether there would be a lower rate of relapse on maintenance doses of trifluoperazine (Stelazine) or chlorpromazine (Largactil) than on a placebo in schizophrenic patients who had recently recovered from an acute episode. The case-notes of all patients admitted to the Bethlem Royal and Maudsley Hospitals and of all Camberwell residents admitted to Cane Hill Hospital were screened. The screening procedure was carried out within a few days of admission and covered the period from April 1968 to December 1969. All patients aged 16 to 55 whose present admission was on account of a possible psychosis were selected, with the exception of those with a first admission more than 10 years previously. They were then interviewed, a standardized clinical examination being used. This is a semi-structured interview known as the Present State Examination (P.S.E.) which has been developed to allow a reliable assessment of patients' symptomatology to be made (Wing *et al.*, 1967; Wing, 1970). The P.S.E. is divided into various sections, such as depressed mood and auditory hallucinations, each containing a number of specific questions. The ratings on certain groups of questions can be summed to produce 35 syndrome scores. A computer program named Catego had been developed which processes the syndrome scores and leads to a standardized clinical grouping. Additional information from the history can also be expressed in a standard form and processed by the Catego program so that it contributes to a final diagnostic grouping.

All patients who were given a diagnosis of schizophrenia by the Catego program from the information obtained from the P.S.E. and the history were potentially suitable for the trial. The consultant psychiatrists involved were contacted and all but one agreed to consider the entry of their patients into the trial. At the time that a potentially suitable patient was discharged the consultant was approached and asked if that patient could be entered into the trial. The potentially suitable patients who were discharged from hospital within the period of the trial formed the base population from which the trial patients were drawn. Patients to whose entry into the trial the consultants agreed were then observed as outpatients for 6 to 12 weeks. Those whose clinical condition had by then stabilized at the pre-admission level were entered in the trial.

Trial patients were allocated at random to an experimental or a control group receiving trifluoperazine 5 to 25 mg or chlorpromazine 100 to 500 mg daily or an appropriate placebo. The allocation to trifluoperazine or chlorpromazine depended on the patient's previous medication, so that so far as the patient was concerned there was no apparent change in treatment. The dose of medication could be varied within the stated limits at the clinician's discretion. An upper limit was stipulated to ensure that a relapse was not treated under the guise of maintenance therapy, and a lower limit was prescribed as it was felt that the drugs were unlikely to be effective at a very low dosage. Anti-Parkinsonian medication could also be prescribed in appropriate doses, as could antidepressant medication. The trial tablets were held by the unit secretary and were dispensed to one of us (J.P.L.), who then gave them to the clinician dealing with the patient just before each outpatient attendance. Only the unit secretary knew which tablets were active drug and which were placebo.

The outpatient care for the trial patients was no different from usual except that a maximum interval of eight weeks between visits was maintained. Most patients were seen every six weeks. The tablets were dispensed in containers of 50 each and the number of containers given out at each visit was noted. The patient was instructed to bring back all containers, whether empty or full, at the next visit. This instruction was also printed on the label of the container. The number of tablets returned at each visit was noted by the clinician, who also asked the patients about the regularity of their taking the drug and recorded his impression on a form. As a further check on drug-taking habits 2 mg of riboflavine was incorporated in the tablets, whether of placebo or active drug. Riboflavine is easily detected in the urine as it produces a green fluorescence when a concentrated beam of light is shone through it (Porter, 1969). A letter was sent to each patient's general practitioner informing him that his patient was taking part in a trial of maintenance therapy and asking him not to prescribe additional psychotropic drugs.

The clinicians were asked to make a very brief assessment of the patients at each outpatient visit and to record this on a form. The criterion of relapse was that the clinician should be sufficiently concerned about the patient's clinical state to want to be certain the patient was on active drug. At this point the patient was automatically withdrawn from the trial and was counted as relapsed. The patient was then re-examined, the P.S.E. being used. If the patient remained well for a year after entry into the trial he was considered to have completed the trial successfully, and the P.S.E. was readministered.

All patients considered potentially suitable for the trial but not entering it were followed up one year after discharge from hospital to determine whether they had relapsed or remained well. For these non-trial patients relapse was defined as a return of schizophrenic symptoms.

CHARACTERISTICS OF TRIAL PATIENTS AND BASE POPULATION

A total of 116 patients who had recovered from an acute schizophrenic illness and had been discharged from hospital were considered to be suitable candidates for the trial. The P.S.E. data available for each patient were processed by the Catego program. In 95 cases the Catego diagnosis was "florid schizophrenia," which indicates that symptoms such as delusions of control, thought insertion, or auditory hallucinations were present (Wing, 1970). In 16 cases the Catego diagnosis was "delusional psychosis," which indicates the presence of various delusions in the absence of nuclear schizophrenic symptoms, auditory hallucinations, or symptoms of affective psychosis. One case was diagnosed as "schizo-affective psychosis" and three as "non-paranoid schizophrenia," which includes catatonic states. In the remaining single case* the Catego diagnosis was "hypomania."

Out of 116 patients who formed the base population only 35 actually entered the trial. Thirty-two of the trial patients were given a Catego diagnosis of "florid schizophrenia." The other three were diagnosed as "delusional psychosis," two of them being in the drug group and one in the placebo group.

The reasons for the remaining 81 patients not entering the trial were: (1) the consultant considered the patient's adjustment too precarious to risk the possibility of placebo being substituted for active drug (15); (2) the consultant considered the patient to have a good enough prognosis not to need maintenance therapy (11); (3) the patient stopped taking medication of his own accord before entering the trial (24); (4) the patient was discharged on a drug other than chlorpromazine or trifluoperazine (12); (5) the patient showed little or no improvement with medication (8); (6) the patient moved away from London or overseas (5); and (7) a miscellany of reasons, such as referral back to the general practitioner for aftercare (6).

It should be noted that the biases operating in groups 1 and 2 would narrow down the trial patients to the middle range of severity of illness if the consultants' assessments of prognosis were correct.

The following items of social and historical data were recorded for each patient: age, sex, colour, intellectual level, peak premorbid heterosexual adjustment and whether any decline had occurred, marital status, length of present marriage, peak occupation, duration of unemployment in previous two years, living group at key date, years at key address, presence of a definite premorbid personality abnormality, age at first onset of psychiatric illness, duration and course since first psychiatric contact, and whether the present episode of illness was the first. There was no significant difference between the trial patients and the non-trial patients on any of these variables. The trial patients did differ from the non-trial patients in terms of the diagnosis given by the Catego programme. There were significantly more patients diagnosed as "florid schizophrenia" in the trial group ($P<0.02$). As stated above, only three of the trial patients were not given this diagnosis. The trial patients did not differ from the non-trial patients on any of the diagnostically important P.S.E. syndromes. The only clinical feature on which they differed from the non-trial patients was in reporting significantly less subjective social withdrawal.

In the trial group the drug patients did not differ from the placebo patients in respect of the Catego diagnosis, the P.S.E. syndromes, or the social and historical data. Thus they are directly comparable, despite the absence of any attempt to match them.

*This patient originally presented with affective symptoms, then after some weeks in hospital she developed a speech disorder typical of schizophrenia. When, as in this case, hypomanic symptoms coexist with disordered speech in the absence of any other schizophrenic symptoms, the Catego program gives more weight to the affective symptoms. However, as the nature of the speech disorder was thought to be characteristic of schizophrenia, the patient was retained in the series. She was not included in the trial because she returned to her general practitioner for aftercare.

Outcome of Trial Patients

Of the 35 patients who entered the trial five subsequently dropped out. One patient relapsed in the first week of the trial and was found to be on placebo. It was concluded that he was already beginning to relapse on entry into the trial and he was counted as a drop-out. He recovered with further treatment and was then considered for the trial again, but the consultant felt he was too precarious to re-enter the trial. Two patients relapsed after a month in the trial and then admitted that they had taken no tablets at all. One was found to have been prescribed active drug and the other placebo. Two other patients stopped taking their medication after a few months and did not return to the outpatient department. They both remained well for at least a year. One had been prescribed active drug and the other placebo.

Of the total of 35 trial patients 15 were found to be on placebo and 20 on active drug. Seven (35%) of the drug patients relapsed—that is, were taken out of the trial at the clinician's request—compared with 12 (80%) of the placebo patients (Table I). The difference in relapse rates is significantly in favour of the active drug ($P = 0.02$). When the patients who dropped out of the trial are removed from the two groups the relapse rates are virtually unchanged (Table I).

TABLE I—*Outcome of Trial Patients*

	Relapsed	Well	Total	Relapse Rate	
Patients Completing Trial Plus Drop-outs					
Patients on placebo	12	3	15	80%	$P=0.02$
Patients on drug ..	7	13	20	35%	
Total ..	19	16	35		
Patients Completing Trial					
Patients on placebo	10	2	12	83%	$P<0.02$
Patients on drug ..	6	12	18	33%	
Total ..	16	14	30		

Of the patients on active drug, 13 were receiving trifluoperazine and five chlorpromazine. Five of the patients on trifluoperazine relapsed compared with one of those on chlorpromazine, a non-significant difference.

The number of patients relapsing in each month of the trial is shown in Table II. The average length of time before relapse is 5·7 months for patients on placebo and 6·5 months for those on active drug, a non-significant difference.

TABLE II—*Length of Time in Trial before Relapse*

Month of trial	1	2	3	4	5	6	7	8	9	10	11	12	Mean
Patients on placebo	1	4				1		1			2	1	5·7
Patients on drug ..		1			1	1	1	1			1		6·5

All the patients who relapsed suffered a recurrence of schizophrenic symptoms similar to those present at the previous admission. The Catego diagnosis made on the basis of the P.S.E. was the same at relapse as at the initial examination for all but one of the relapsed patients. This patient had an initial Catego diagnosis of "florid schizophrenia" and a diagnosis at relapse of "delusional psychosis." All the patients on active drug who relapsed were readmitted to hospital, whereas only half of those on placebo were readmitted. The remaining placebo patients were treated with drugs as outpatients and recovered.

DRUG DOSAGE

The daily dose of chlorpromazine or its placebo varied from 100 to 300 mg, 6 of the 13 patients being maintained on 100 mg daily. The mean daily dose of drug was 157·1 mg and of placebo 158·3 mg. The daily dose of trifluoperazine or its placebo varied from 5 to 15 mg, 10 of the 22 patients being maintained on 15 mg and 11 on 10 mg daily. The mean daily dose of drug was 12·3 mg and of placebo 11·7 mg.

CHECKS ON DRUG TAKING

Despite considerable encouragement patients were unreliable in bringing back their remaining tablets to be counted. Testing of the urine for the presence of riboflavine proved to be a more satisfactory check on drug taking. Out of 187 visits to the outpatient department when a urine specimen could have been obtained, a satisfactory specimen was tested on 117 occasions (63%). In 110 cases the urine test was positive and the tablet count was either in agreement or else could not be done. In one case the urine test was negative and the patient admitted to taking no tablets at all. He was therefore dropped from the trial. In three cases the urine test was negative but the tablet count suggested that the patient was taking his medication as prescribed. In all of these the urine specimen was dilute and the patient was on a relatively low dose of medication. In three further cases the urine test was positive but the tablet count suggested considerable defaulting. Taking into account the false-positive and false-negative results, the reliability index for the test is 111 out of 117 or 95%.

The fact that virtually all the patients were reliable in taking their medication as prescribed, in contrast to previous findings on outpatient populations, emphasizes the highly selected nature of the trial group.

ADDITIONAL MEDICATION

In addition to the trial drugs, anti-Parkinsonian and antidepressant medication was prescribed for some of the patients. Ten out of 15 patients on placebo received anti-Parkinsonian medication compared with 13 out of 20 patients on active drug, a non-significant difference. Side effects did not prove troublesome in any patient and therefore the doctors concerned probably received no clues about whether the patient was on active drug or not.

Antidepressant medication was prescribed for four patients, all of them on active drug. In fact, all were receiving trifluoperazine, but the numbers are too small for the difference from the placebo patients to reach significance. One patient was given an antidepressant as part of her initial treatment in hospital and continued on it throughout the trial. Another patient was prescribed an antidepressant after several months in the trial and relapsed shortly afterwards with a schizophrenic episode in which depressive features were prominent. One patient developed depressive delusions and another developed depressive hallucinations in the course of the trial. The symptoms of both patients responded to an antidepressant drug and they completed the trial without relapse.

Outcome of Non-trial Patients

An attempt was made to follow up all the patients who formed the base population but who did not enter the trial for the reasons given above. The follow-up was conducted one year after the patient's discharge from hospital. Information was obtained from case-notes of current patients, from other hospitals to which patients were admitted, from general practitioners, and from the patients' relatives. Satisfactory information was obtained for 77 of the 81 patients, a 95% success rate. The outcome for the various groups is given in Table III.

TABLE III—*Outcome of Non-trial Patients*

Group	Relapsed	Well	Not Traced	Total	Relapse Rate
1. On drugs, too precarious to enter trial ..	10	5	0	15	66·7%
2. Not on drugs, doctor's action (too well for trial)	3	8	0	11	27·3%
3. Not on drugs, patient's action	16	8	0	24	66·7%
4. On different drug ..	8	4	0	12	66·7%
5. Not improved by medication	7	0	1	8	87·5%
6. Moved away (on drugs)	0	2	3	5	—
7. Miscellaneous ..	2	4	0	6	33·3%
Total ..	46	31	4	81	56·8%

The overall relapse rate in the non-trial patients was 56·8% compared with a relapse rate of 53·3% in the trial patients. The similarity of these figures cannot be taken to imply that the trial patients are a representative sample of the base population. On the contrary, it is evident from the differential relapse rates of the various subgroups that they form distinct clinical entities. The relapse rate of the patients considered to have a good enough prognosis not to need maintenance therapy (group 2) was significantly lower (exact $P = 0.048$) than that of the patients thought to be too precarious for the trial (group 1). The relapse rate of the patients in group 2, who were kept off drugs, was also significantly lower than that of the trial patients on placebo (exact $P = 0.01$). The relapse rate of the patients in group 1, who were maintained on drugs, was double that of the trial patients on active drug, though the difference just fails to reach significance. These findings indicate that the clinicians involved were giving fairly accurate prognoses, and it is noteworthy that these are the pooled patients of 12 different psychiatrists. In addition, the results show that the trial patients were indeed intermediate in prognosis between the non-trial patients of groups 1 and 2.

BASIS OF PSYCHIATRISTS' PROGNOSTICATIONS

In an attempt to discover the basis on which the psychiatrists were making valid prognostic distinctions between the groups, these were compared by using the items of social and historical data listed above, the Catego diagnosis, and the P.S.E. syndromes. It was found that the patients with a good prognosis (group 2) differed significantly from the precarious patients (group 1) and the trial patients by showing more auditory hallucinations and more features of "endogenous" depression (including early waking, morning depression, guilt, and self-depreciation; depressed mood as such was not discriminatory). They were significantly more likely to be suffering from their first episode of illness, to have a shorter duration of illness, and to have a good premorbid personality.

The 12 consultants involved in the trial were asked to specify which features of schizophrenia they thought were linked with a good outcome. Ten of them replied, and five of these mentioned at least three of the above items which were found to discriminate between the groups. All of them included at least one of the above items. There was greatest unanimity on an acute onset, a good premorbid personality, and pronounced affective

symptoms. Only two psychiatrists mentioned a first episode and two specified auditory hallucinations.

EFFECT OF MAINTENANCE THERAPY ON NON-TRIAL PATIENTS

At the follow-up of the non-trial patients reasonably reliable information was obtained about their drug taking throughout the preceding year. It was easy to assign patients who were not prescribed drugs to the group not on maintenance therapy. It was less certain that those who were prescribed drugs took them regularly. The only information available was the clinicians' comments in the case-notes, and these suggested that virtually all the patients judged to be precarious took their medication regularly. The relapse rate in the group who seemed to take their drugs regularly can be compared with that in the group who were not on drugs or who failed to take them (Table IV).

TABLE IV—*Effect of Drugs in Non-trial Patients*

	Relapsed	Well	Total	Relapse Rate
Patient on drugs ..	26	14	40	65·0%
Patient not on drugs ..	20	17	37	51·1%
Total ..	46	31	77	

The group on drugs did rather worse than the group who took no medication. This result is understandable in view of the nature of the subgroups. The patients given a good prognosis did well without drug treatment and the patients given a bad prognosis did badly despite drug treatment.

PATIENTS WHO DISCONTINUED MEDICATION

The patients in group 3 were those who discontinued medication themselves shortly after discharge and before there was a chance of entering them in the trial. The group as a whole had a high relapse rate (66·7%). It is possible that many of the 16 patients who relapsed would have remained well if kept on maintenance therapy. It would be useful to be able to identify potential defaulters so that extra effort could be directed at keeping them on drugs, perhaps by using long-acting injections. The patients in group 3 were found to differ significantly from the rest of the base population in the following respects: they were younger, more often single, more of them were males, and more of them showed a decline in their heterosexual adjustment; they were also more likely to suffer from situational anxiety, and this may have been a factor in preventing their attendance at clinics.

Discussion and Conclusions

This placebo-controlled, double-blind trial has shown that the use of phenothiazines during one year of maintenance therapy in a selected group of schizophrenic outpatients is significantly more effective than a placebo in preventing relapse. Nevertheless, one-third of the patients known to be taking active drug regularly relapsed. It is possible that the serum levels of drug in these patients were not adequate, and this issue needs further study. An important question arising from the above result is how far it can be applied to all schizophrenics. It must be kept in mind that the patients forming the base population were all acute schizophrenics with a recent episode of illness and that in this study a relatively narrow definition of schizophrenia has been used. Hence, the findings cannot be generalized to chronic schizophrenia or to schizophrenia as defined by most American psychiatrists. In addition, the applicability of the result depends on the relationship between the trial patients and the group from which they were selected. The data collected on the base population showed that the patients selected by their consultants to enter the trial were those with an intermediate prognosis. The patients rejected for the trial included a group who were considered to be well enough not to need maintenance therapy and a group who were thought to be too precarious to risk taking them off drugs. The prognoses given by the consultants turned out to be substantially correct, and the analysis of the data showed that the clinical features on which they said they were basing their prognosis did in fact discriminate between the various groups.

The follow-up showed that most of the patients given a good prognosis remained well without any drugs, while most of those given a bad prognosis relapsed despite being kept on drugs. Maintenance therapy cannot confidently be said to play an important part in either of these two groups. A similar conclusion can be drawn from the outcome of the whole group of non-trial patients as there was no significant difference in relapse rates between those on drugs and those on no therapy.

There is a choice of two therapeutic strategies: either to give blanket maintenance therapy to all schizophrenic outpatients in an attempt to cover that proportion of the population that is likely to benefit or to try to exclude those patients for whom maintenance therapy is a waste of time and money. There is an additional consideration, apart from the temporal and financial ones, that must influence the choice of strategy. There are definite hazards associated with long-term phenothiazine treatment. Irreversible and incapacitating dyskinesias can develop, serious pigmentation of the cornea and lens can occur, and there have been reports of cardiovascular complications including dysrhythmias and disturbances of conduction (*British Medical Journal*, 1971). These are cogent reasons for attempting to expose as few people as possible to long-term phenothiazines.

The data in this study do not enable us reliably to identify the patients who are likely to relapse despite taking prophylactic medication. On the other hand, there are pointers to the patients who are likely to remain well for at least a year without any drug treatment. These are patients in a first episode of illness with an acute onset, whose clinical state includes symptoms of "endogenous" depression, and who had a good personality before the onset of the illness. It might be considered justifiable to withhold maintenance treatment from such patients. There is not much evidence that the most severely ill patients benefit either, but there is a group intermediate between these two extremes for whom maintenance phenothiazine treatment is of value. Only the clinician can decide where to draw the line. However, particular attention should be concentrated on the potential defaulters, who are likely to be young unmarried men who have shown a decline in their heterosexual adjustment and who may suffer from phobic symptoms.

The results of this trial sound a warning note for other drug studies. The patients selected to take part in the trial were shown to be those most likely to benefit from treatment. Unless trial patients are viewed in the setting of the population from which they are selected, the conclusions drawn about therapeutic efficacy may be overoptimistic.

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References

Åsberg, M., Cronholm, B., Sjöqvist, F., and Tuck, D. (1970). *British Medical Journal*, 4, 18.
British Medical Journal, 1971, 1, 3.
Cole, J. O. (1964). *Archives of General Psychiatry*, 10, 246.
Curry, S. H., Davies, J. M., Janowsky, D. S., and Marshall, J. H. L. (1970). *Archives of General Psychiatry*, 22, 209.
Diamond, L. S., and Marks, J. B. (1960). *Journal of Nervous and Mental Disease*, 131, 247.
Engelhardt, D. M., and Freedman, N. (1970). In *Social Psychiatry*, ed. A. Kiev, vol. 1. London, Routledge and Kegan Paul.
Engelhardt, D. M., *et al.* (1960). *Journal of the American Medical Association*, 173, 146.
Engelhardt, D. M., *et al.* (1963). *Journal of the American Medical Association*, 186, 981
Engelhardt, D. M., Freedman, N., Rosen, B., Mann, D., and Margolis, R. (1964). *Archives of General Psychiatry*, 11, 162.
Gibberd, F. B., Dunne, J. F., Handley, A. J., and Hazleman, B. L. (1970). *British Medical Journal*, 1, 147.
Good, W. W., Sterling, M., and Holtzman, W. H. (1958). *American Journal of Psychiatry*, 115, 443.
Gross, M. (1960). *American Journal of Psychiatry*, 117, 444.
Kendell, R. E., *et al.* (1971). *Archives of General Psychiatry*. In press.
Luntz, G. R. W. N., and Austin, R. (1960). *British Medical Journal*, 1, 1679.
Parkes, C. M., Brown, G. W., and Monck, E. M. (1962). *British Medical Journal*, 1, 972.
Pasamanick, B., *et al.* (1964). *Journal of the American Medical Association*, 187, 177.
Porter, A. M. W. (1969). *British Medical Journal*, 1, 218.
Rathod, N., and Rees, L. (1958). *Journal of Mental Science*, 104, 705.
Shawver, J. R., Gorham, D. R., Leskin, L. W., Good, W. W., and Kabnick, D. E. (1959). *Diseases of the Nervous System*, 20, 452.
Willcox, D. R. C., Gillan, R., and Hare, E. H. (1965). *British Medical Journal*, 2, 790.
Wing, J. K. (1970). In *Symposium on Psychiatric Epidemiology*, ed. E. Hare and J. K. Wing. London, Oxford University Press.
Wing, J. K., Birley, J. L. T., Cooper, J. E., Graham, P., and Isaacs, A. D. (1967). *British Journal of Psychiatry*, 113, 499.

Slow Sodium: An Oral Slowly Released Sodium Chloride Preparation

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Summary

The use of a slowly released oral preparation of sodium chloride is described. It was given to patients and athletes to treat or prevent acute and chronic sodium chloride deficiency. Gastrointestinal side effects were not encountered after the ingestion of up to 500 mEq in one day or 200 mEq in 10 minutes.

Introduction

Sodium depletion, with the fluid loss with which it is usually accompanied, produces symptoms which are well described (King and Barry, 1962; Leithead and Lind, 1964): headache, thirst, anorexia and nausea, apathy, drowsiness, postural giddiness, and muscle cramps. Eventually the blood pressure falls and death may ensue from peripheral circulatory failure.

In temperate climates this picture is commonly seen only in patients with uncompensated loss of gastrointestinal secretions, in patients with renal damage subjected to dietary salt restriction, or with over-enthusiastic use of diuretic drugs. Occasionally it may appear in Addisonian crisis, in uncontrolled diabetes, or with cerebral lesions. Treatment is usually by intravenous saline infusion after the patient has been admitted to hospital. This, however, does not give a true picture of the extent of the problem of sodium depletion throughout the world. For many people in certain climatic conditions or in certain occupations, such as coal miners and gold miners (King and Barry, 1962), seamen in tropical waters (Stenning, 1945), or the armed Forces abroad, the fight against incipient salt and water depletion may be continuous.

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In theory an increased salt and water intake should prevent depletion. But though people regularly subjected to prodigious sweat loss eventually achieve overall sodium and water balance, they may still suffer from a steady state of sodium depletion or the daily recurrence of a transient salt depletion syndrome. This problem is particularly acute in individuals who are not acclimatized (Leithead, Leithead, and Lee, 1958). It is then easy to acquire a pronounced initial salt and water deficit which may take days to correct. During this time physical perfomance will be much lowered. This was strikingly illustrated in the 1970 World Cup football competition in Mexico. Training for and playing football in temperatures approaching 100°F (37·8°C) produced a noticeable weight reduction due to sweat loss, which was not necessarily regained in spite of deliberate attention to salt and water replacement. For this reason a few players of some of the national teams in the competition were incapacitated for several days.

There has been no effective way to administer large quantities of sodium chloride orally (Leithead and Lind, 1964). Saline solutions are unpalatable. Enteric-coated tablets are notorious in that they are excreted unchanged in the faeces (Leithead *et al.*, 1958). Some years ago therefore we asked the Ciba pharmaceutical company to prepare slow release sodium chloride tablets using the wax sponge formulation they had introduced for their potassium supplement preparation Slow-K. We here report the results of some of our experimental work with these tablets and clinical experience over several years. This preparation, which has been named Slow Sodium (sodium chloride 600 mg, equivalent to 10 mEq Na^+ and Cl^-) was also used by the English international football team in Mexico in 1970 where it proved very successful in solving the problem of salt and water depletion.

Balance Studies

Tests were first carried out in vitro to ensure that if the tablets should pass through the gut unchanged they would be detected in the faeces by our analytical technique. Tablets of Slow Sodium were added to a sample of homogenized faeces. The faeces and tablets were then homogenized for a further 20 to 30 minutes, which is the time normally taken to homogenize a five-day faecal collection. Sodium in the faeces both before and after the