Brit. J. Psychiat. (1981), **139**, 89–101

Studies of Depressive Symptoms in Schizophrenia
I. The Prevalence of Depression and its Possible Causes

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Summary: Depression assessed by clinical examination and Hamilton rating scale was found in half of 37 untreated new acute schizophrenics, and in about a third of chronic schizophrenics who relapsed whether treated with depot injections (89) or not (79). A significant part of depressive illness in schizophrenics is thus not drug-related. However, depression was commoner in those on higher doses of depot neuroleptic ($P < .05$) or who showed extrapyramidal side effects ($P < .001$), suggesting that drugs can play a part. Patients maintained in remission on moderate doses of depot drug had the lowest prevalence of depression.

The presence of depressive mood disorders in schizophrenia have been recognized since the days of Kraepelin and Bleuler. In particular it has been suggested that patients may manifest a depressive syndrome when their psychosis has abated (Mayer-Gross, 1920; Claude *et al*, 1924; Claude, 1930; Semrad, 1966; Steinberg *et al*, 1967; Bowers and Astrachan, 1967; Roth, 1970; Donlon and Blacker, 1973; Rada and Donlon, 1975; McGlashan and Carpenter, 1976a; 1976b; Mackinnon, 1977; Docherty *et al*, 1978). However, it is clear from assessments of patients established on treatments for lengthy periods that the frequency of depression is high even after long periods in remission (Leff and Wing, 1971; Hirsch *et al*, 1973; Knights *et al*, 1979). The neuroleptic drugs have been alleged to have a depressant effect in some patients, particularly certain depot preparations (Alarcon and Carney, 1969; Falloon *et al*, 1978), but this is unlikely to be a simple relationship since in some double-blind controlled trials the placebo group has experienced an identical frequency of depression as the active drug recipients (Leff and Wing, 1971; Hirsch *et al*, 1973). A number of trials even suggest that chlorpromazine may have an antidepressant effect (Brockington *et al*, 1978). The possible contribution of drugs to mood disorders in schizophrenia is complicated further by the existence of a syndrome resembling depressive illness which occurs in association with drug induced parkinsonism. Recently a number of authors (Klein and Davis, 1969; Rifkin *et al*, 1975; Van Putten *et al*, 1978) have drawn attention to this frequently overlooked syndrome. Ayd (1975) speculates that such depressions are an affective manifestation of an extrapyramidal reaction. The suicide risk of a schizophrenic is 50 times that of a normal population (Markowe *et al*, 1967), but studies have failed to show any direct causal relationship between neuroleptic medication and suicide in schizophrenia (Farberow *et al*, 1961; Cohen *et al*, 1964). In one series some suicides occurred shortly after the patients' phenothiazines had been stopped (Cohen *et al*, 1964). It is also claimed that some patients experience a prodromal phase of schizophrenia, before treatment has been instituted, which may be indistinguishable from endogenous depression (Conrad, 1958).

Despite the frequency (Knights *et al*, 1979) and complexity of depressive syndromes in schizophrenia it is a subject that has received little systematic or prospective study, particularly in patients on regular neuroleptic medication. The correct treatment of these depressive syndromes, and in particular the validity of the commonly adopted clinical practice of using tricyclic antidepressants is quite unexplored. With the possible exception of Prusoff *et al* (1979) there are no published prospective double-blind controlled trials specifically designed to test the effect of tricyclic antidepressant drugs in adequate doses on a recently developed depressive mood disorder in a schizophrenic patient maintained in remission with neuroleptic drugs.

Method

The patients included in these studies were consecutive patients at one of two hospitals (University Hospital of South Manchester or the North Man-

chester General Hospital), and the examinations were carried out over an eight year period, by the author unless otherwise stated. The diagnosis of schizophrenia was based upon the presence of Schneiderian first rank symptoms either at the time of the interview or previously recorded in the notes (Mellor, 1970).

For the purposes of these studies depression was defined as a change of affect so that the patient had a lowered mood state, with subjective changes of sadness, misery, tearfulness or hopelessness. The aim was to record depression as present only if it could reasonably be regarded as clinically meaningful and likely to provoke some treatment adjustment or other intervention. Therefore, unless otherwise stated in the individual sample description, all patients were diagnosed as clinically depressed for a minimum period of one week. The severity of depression was rated on the Beck Depression Inventory (BDI) and Hamilton Rating Scale for depression (HRS(D)) and patients were only included in the studies if they scored a minimum of 15 on one of these scales. The HRS(D) was completed for all patients; because of the severity of clinical disturbance not all patients were able to complete the self-rating BDI. The author's own clinical diagnosis of depression was previously validated against the BDI in a non-psychotic population: no depression score = 0–10; mild depression = 11–18, mean 14.5, S.D. 6.4; moderate depression >18, mean 22.4, S.D. 5.6 (Johnson and Heather, 1974; Johnson and Mellor, 1977).

All patients had their mental symptoms scored on the BPRS (Overall and Gorham, 1962) and the presence of extrapyramidal symptoms determined by an examination based on the EPRS (Simpson *et al*, 1964). All assessments were completed within forty-eight hours of admission.

Four types of patients were evaluated (see Table I).

(a) First illness schizophrenia: Consecutively admitted in-patients who had not been prescribed neuroleptic medication prior to admission. These patients presented in one of three ways. Some were referred with an acute behaviour problem through the social services or police, or through the casualty department. A few patients were initially referred with a diagnosis of depression or personality disorder; and a few without diagnostic assessment. In each case the absence of previous neuroleptic medication was carefully confirmed by enquiry. Depression was recorded as present or absent at the time of admission, and if absent at this time whether present in the previous two months. Although five of the eleven patients included in the survey were actually attending the hospital at the time of the relevant depressed mood they did not have a BDI or HRS(D) score, but like the other patients with a history of depression these patients had a history of a change of social functions secondary to their altered mood state. The changes were of sufficient severity to be equivalent to a BDI score of 19, an equivalence previously validated (Johnson and Mellor, 1977).

(b) Patients admitted in acute relapse but not on drugs. These patients were all chronic schizophrenic patients with two or more previous admissions for acute schizophrenia. Patients were only included in this drug-free group if they had taken no oral neuroleptic medication for two months, or received no depot neuroleptic injection within the preceding three months. In most cases the duration was much longer.

(c) Patients admitted in acute relapse while on regular depot neuroleptic injections. These patients were all chronic schizophrenic patients with two or more previous admissions for acute schizophrenia. Patients were only included in this sample if they were on regular depot medication, the most recent injection within four weeks before admission.

(d) Three groups of patients maintained on regular depot neuroleptic injections and free from acute symptoms:

(i) The prevalence for a two-month period was determined by the random selection at the depot injection clinic of patients who had been well without relapse for a minimum of three months, and by conducting two mental state examinations at an interval of two months.

(ii) Patients prescribed antidepressant medication during a 15 month prospective assessment for the treatment of extrapyramidal symptoms (Johnson, 1973).

(iii) Random selection by the nursing staff of chronic schizophrenic patients maintained free of acute symptoms on regular depot injections for a minimum period of three months as an out-patient. Each patient was interviewed by the nurses with a standardized interview and rated on a five point scale of clinical depression (0–4). In addition each patient completed two self assessments of their mood state over the previous week. One assessment was on a linear scale (Depression–Normal–Elation) and the other on a five point scale of depression (0–4). The acceptance that depression had been present for a minimum of one week was based on a combination of the nurses' and patients' assessments. The patient had to rate at least mildly depressed (score = 1) on each scale, and also score a minimum total of four on the three scales.

Results

The prevalence and severity of depression in each sample of patients is summarized in Table I.

All patients studied were 17–65 years of age. The

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TABLE I

Prevalence of depression in schizophrenia

	Sample N	Depression present	BDI ratings 15–19	BDI ratings 20–24	BDI ratings >25	HRS 15–19	HRS 20–25	HRS >25
(a) First illness schizophrenia. No previous drugs								
Depression present on admission	37	7	4	1	0	4	2	1
History of depression in previous two months	30	11	–	–	–	–	–	–
Total depression	37	18	–	–	–	–	–	–
(b) Chronic schizophrenia: Relapse, not on drugs	79	24	2	2	1	14	8	2
(c) Chronic schizophrenia: Relapse, on depot medication	89	34	14	9	4	16	14	4
(d) Patients in remission on depot medication								
2 month prospective study of random sample	41	10	3	7	0	4	6	0
15 month survey of prescribed antidepressants	140	21	–	–	–	–	–	–
Nurses' survey of random sample	100	26	–	–	–	–	–	–

mean age of patients with a first illness (21.7 years) was younger than the mean ages of the other groups (27–31 years). In all groups there were an excess of female patients (51–64 per cent) except the chronic schizophrenic patients relapsing on drugs where there was an excess of males (56 per cent).

Only two depot preparations were used for the patients on regular medication (fluphenazine decanoate N = 176; flupenthixol decanoate N = 112). No other form of neuroleptic drug was used, except occasionally in acutely relapsed patients. There was no difference in the frequency or severity of depression between patient groups on the two drugs.

An analysis of dose schedules and the presence of depression showed less depression with lower dose in all groups but this only reached a level of significance ($P < .05$) in the patients with an acute relapse when the highest dose range was compared with the lowest (Table II).

TABLE II

Dose of long acting depot neuroleptic and presence of depression in schizophrenic relapses

Dose in weekly equivalents of decanoate	Number of patients in Sample	Number of patients in Depression
Fluphenazine > 12.5 mg or flupenthixol > 20 mg	27	16
Fluphenazine = 12.5 mg or flupenthixol = 20 mg	49	16
Fluphenazine < 12.5 mg or flupenthixol < 20 mg	13	3

An analysis of the Brief Psychiatric Rating Scale (BPRS) scores and depression revealed no significant correlations either in the comparison of total scores (Table III) or in individual items other than the depression score. Overall the presence of extrapyramidal symptoms was significantly related to the presence of depression ($P < .001$) although not statistically significant in each sub-group observed. There was also a trend, not reaching significance, for more severe extrapyramidal symptoms to correlate with more severe depression.

The prevalence of depression was lowest amongst the patients maintained in remission by regular depot neuroleptic injections (Table I) and this is highly significant ($P < .02$) if compared to the group with highest level of depression.

Discussion

The results clearly suggest that, although the emphasis may vary, depression is a frequent symptom

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TABLE III

Brief psychiatric rating scale scores in schizophrenic groups as a whole and with depression

BPRS	Acute relapse				In remission	
	On drugs		No drugs		Maintenance drugs	
	Sample N	Depression N	Sample N	Depression N	Sample N	Depression N
> 30	7	3	2	0	0	0
21–30	25	8	12	6	2	1
10–20	55	21	63	18	17	6
< 10	2	2	2	0	81	19
Total	89	34	79	24	100	26

No significant relationship between BPRS scores and depression.

TABLE IV

Extrapyramidal symptoms and depression

Patients	Sample N	EP present		EP absent		P
		Dep.	Not Dep.	Dep.	Not Dep.	
Prescribed antidepressants in remission	140	13	34	8	85	N.S.
Random sample in remission	41	8	16	2	15	N.S.
Nurse sample in remission	100	16	12	10	62	N.S.
Admissions in relapse	89	20	22	14	33	N.S.
Total patients	370	57	84	34	195	< .001

EP = extrapyramidal; Dep. = depressed. Numbers, patients in each category.

in the course of a schizophrenic illness, and likely to be present in all phases, first illness, relapse whether or not on drugs, and even in patients maintained in remission on regular depot neuroleptic injections. The high prevalence of depression in drug-free patients, both first illness patients and relapsed chronic schizophrenics, demonstrates that a significant proportion of depressive symptoms are not drug-related. However some depressive symptoms may be drug-related since both high dose of medication and the development of drug induced extrapyramidal symptoms correlate at a level of significance with the presence of depression. In the literature the association between dose of medication and depression is unclear (Van Putten *et al*, 1978), but this may be because of an unknown level of non-compliance with oral medication.

It is important to note that the patients maintained in remission on regular depot injections had the lowest prevalence of depression. This needs an explanation. It could indicate that the successful treatment of the acute psychosis reduces the risk of depression, even if there is a short-term risk of an immediate post-psychotic depression. This reduced risk is not due to the resolution of schizophrenic symptoms alone: there was no correlation between either the total BPRS score or the scores on individual items other than depression and presence or absence of depression (Table III). This agrees with the report by Brockington *et al* (1978) who also observed a dissociation between improvement of schizophrenic and affective symptoms. Possibly the affective symptoms are an intrinsic part of the schizophrenic illness and resolve as the total illness is controlled, at least at a

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symptomatic level. It could also be argued that neuroleptics have a specific antidepressant action, but this is contrary to the observation that the risk of depression is increased by a higher dose of neuroleptic, unless one supposes that there is a different effect at different dose levels and that patients once in remission are maintained on lower doses. The best prognosis is likely to be achieved for our patients in relief from depression if the lowest dose prescription necessary to maintain remission is used and attention to the early removal of extrapyramidal symptoms is maintained. It is possible that not all symptoms of depression are in fact related to the same underlying process. The difficulty of separating drug-induced akinesia from depression has been recently highlighted, and the present survey does not necessarily separate these two syndromes.

It is difficult to place the results of these studies in the perspective of other results since depression has previously only been studied as one aspect of a drug trial and the samples studied have not usually been restricted to either acutely ill patients or patients in full remission. However, two recent studies monitored depression in drug maintained out-patients (Falloon *et al*, 1978; Knights *et al*, 1979) for twelve and six month periods respectively and both noted depression in approximately half the total patient sample. In one study more patients required in-patient treatment for depression than for schizophrenic relapse (Falloon *et al*, 1978).

II. A Two-year Longitudinal Study of Symptoms

Summary: Following 30 schizophrenic patients over a two-year period confirmed the frequency of depressive symptoms during both acute relapse and remission while on regular depot neuroleptic maintenance therapy. The duration of morbidity from depression alone was over twice as long as from schizophrenic symptoms alone or in combination with depression. The study failed to identify any association between the development of depression and life events, treatment changes or the development of new extrapyramidal symptoms in individual patients.

The previous paper (study I) reported the frequency of finding depression on a single occasion in samples of patients under different conditions of relapse, remission and treatment. This throws light on the prevalence of depression within a schizophrenic population and suggests causative associations, but it does not indicate either the frequency or duration of depressive symptoms in an individual patient. It does not tell us whether a finding of depression on the first interview always means a period of depressive illness or whether depression is always associated with a particular event or circumstance. It was therefore decided to follow up a small group of chronic schizophrenic patients in closer detail over a period of two years.

Method

Chronic schizophrenic patients who relapsed while on regular medication were monitored for 24 months from the time of re-admission. The survey was carried out with consecutive admissions in modules of five patients, because of service commitments, until a sample of 30 patients had completed the two year period. All operational definitions were the same as for study 1, but the patients involved were a separate sample.

At the time of admission information was obtained from relatives, and from the patients when possible, in a semi-structured interview by the author using the check list and procedure of Paykel *et al* (1971). Life events were continuously monitored for the period of the study at regular monthly appointments, but specific confirmation was obtained from relatives for the period of one month before any subsequent relapse into either schizophrenic symptoms or depression.

All patients were prescribed regular depot neuroleptic injections, the only other drugs allowed being occasional oral neuroleptics during a period of relapse, anti-parkinsonian drugs only in the presence of extrapyramidal symptoms, and a benzodiazepine drug for sleeping in rare instances.

An episode of depression was recorded when the patient developed depression according to the criteria for Study 1, and the episode recorded as ended when the Beck Depressive Inventory (BDI) score fell to ten. The higher BDI score of fifteen for entry was to ensure that the mildest of depressive

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mood changes were excluded, but since the score of ten is the generally accepted cut-off (Johnson and Heather, 1974) it was thought reasonable to use this score to indicate the end of an episode of depression.

A relapse of schizophrenia was defined as the appearance of a new schizophrenic symptom, the need to alter management because of an increase of schizophrenic symptoms, or an increase of 15 per cent in the total BPRS score excluding the mood items of depression and grandiosity. The episode was recorded as terminated when a substantial reversal of the entry criteria had taken place.

All patients were seen at intervals of one month by the author routinely for assessment; in addition they were screened by the nurses at the time of each injection and referred for more detailed assessment if indicated.

Results

Thirty-five patients entered the study. Two patients defaulted from treatment and three left the area. The patients treated were all between 19–63 years of age (80 per cent 19–40; 20 per cent 41–63 years; mean age 27.8 years). Eighteen patients were female of whom five were living with marriage partners, nine with other relatives, two in flats, one in a boarding house and one in a hostel. Two males were living with marriage partners, two in boarding house type accommodation and the rest with relatives.

During the two year survey (periods of maintenance and relapse) a total of 21 patients experienced depression (70 per cent). At the time of the schizophrenic relapse leading to inclusion in the sample (N = 30), 18 patients (60 per cent) were actually depressed. During the period of maintenance therapy following the recovery from acute symptoms (mean 21.5 months) five patients experienced a single depression and a further 11 patients had more than one episode of depression (Table I). A total of 50 separate episodes of depression of more than one week's duration occurred during the maintenance period.

Of the 11 patients who had multiple new depressions (see Table I) developing during the survey period, only three had the same variables (Table II) in the preceding month each time. In one a life-event occurred before each of three depressive episodes, in two others none of the listed variables were found in any of the four episodes.

During the two-year period on depot injections there were 14 episodes of acute schizophrenic deterioration shared by nine patients. One patient had three schizophrenic relapses, three patients experienced two relapses and five patients each had a single relapse. Each schizophrenic relapse was accompanied by an episode of depression either at the time of relapse or during the following month. The changes of social functioning associated with these episodes is shown in Table III.

The duration of time that acute or positive schizophrenic symptoms and depressive symptoms were present were calculated separately for the period from initial discharge from hospital until the completion of

TABLE I

Amount of depression in chronic schizophrenics during 21.5 months mean maintenance

New episodes of depression in maintenance period	In-patients (N = 30)	Total episodes
1	5	5
2	1	2
3	2	6
4	4	16
5	3	15
6	1	6
Total	16	50

Each depressive episode lasted at least one week.

TABLE II

Events in the month preceding a depressive episode in 30 patients

	Depressive episodes (total N = 50) with event noted	
	N	
Change of mental state	14	
New extrapyramidal symptoms	8	
Life event	24	
Change of drug therapy	6	
[None of the above	20]	(40%)

33 episodes had only one of the four possible events, 12 had two, and 5 had three.

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TABLE III

Change of social function with depressive and schizophrenic relapses

	Depression N		Schizophrenia N		
	At risk	Change	At risk	Change	Total affected
Patients employed who stop work	9	7	4	4	11
Patients unemployed who deteriorated in work pattern (O.T. etc.)	7	5	5	5	10
Environment changed	21	18	9	9	27
Compulsory admission—Mental Health Act	21	0	9	3	3
Relatives reported substantial deterioration	21	11	9	9	20

Total patients with depression = 21.
Total patients with schizophrenic relapse = 9.

the study (mean duration = 21.5 months). For a schizophrenic relapse the mean duration was 12 weeks from 14 separate relapses in 9 patients. The mean duration of depression was 8.4 weeks with 50 separate new episodes in 16 patients. On occasions both symptoms were present at the same time (64 weeks out of a total period of morbidity with symptoms present of 524 weeks from all patients). Depression alone was responsible for morbidity in 356 weeks (70 per cent of total morbidity), schizophrenia alone for 104 weeks (20 per cent) and mixed symptoms for 64 weeks (10 per cent).

Discussion

The results of this longutidinal study on a separate sample confirm the results of the point prevalence studies (Study 1) that depression is a frequent symptom both during relapse (60 per cent) and maintenance therapy (50 per cent). The results are almost identical to the frequency reported by Falloon *et al* (1978), and Knights *et al* (1979), although the duration monitored in this study was longer. The results clearly suggest that for patients maintained on regular depot injections the risk of a new episode of depression was three times as great as the risk of an acute schizophrenic relapse. The duration of morbidity from depression alone was over twice as long as the duration of morbidity from either acute schizophrenic symptoms alone or in combination with a depressed mood. However an examination of Table III will emphasize that a schizophrenic episode is likely to produce a greater severity of illness with a much greater disruption of life since it more frequently results in total cessation of all work, admission to hospital and the use of compulsory powers under the Mental Health Act. Relatives in particular tolerate a schizophrenic deterioration less well.

A little under one third of the sample remained free from depression both during relapse and in remission so it is possible that a minority of patients are less vulnerable to depressive symptoms whatever the aetiology. An analysis of a limited number of possible causative associations fails to identify any consistent relationship between any of the variables monitored and depression. In only three patients was the presence or absence of possible associations consistent in all depressions experienced by a particular patient. This must suggest that in individual patients the cause of depression varies on different occasions, or that the natural history of the illness, or some other factors not monitored, are important dependent variables in the causation of depression. It is probable that both hypotheses are correct and that causation is a varying and complex problem. In this study no attempt was made to identify the drug-induced akinesia syndrome, which may mimic depression in presentation, so the identification of true depression may have been over-estimated, but consideration of this problem is dealt with in the next study.

These results emphasise the need to consider the symptom of depression carefully in the treatment of schizophrenia. It is most unlikely that there is a single

cause, even in individual patients, and consequently it is equally unlikely that a single treatment whether neuroleptic drug manipulation, the addition of antidepressants or other drugs, or social therapy will bring universal relief. Depression requires individual evaluation in each patient.

III. A Double-blind Trial of Orphenadrine against Placebo

Summary: A double-blind trial of orphenadrine 50 mg twice daily in the treatment of 40 depressed schizophrenic patients, maintained in remission with depot neuroleptic injection and free from overt extrapyramidal symptoms, showed a small non-significant excess of patients whose depression improved on orphenadrine. These patients experienced significantly more muscular weakness and stiffness, and may have had neuroleptic-induced akinesia rather than true depression.

A number of authors have described the syndrome of neuroleptic-induced akinesia and have emphasised the difficulty in distinguishing this syndrome from depression or from the negative symptoms of schizophrenia (Rifkin *et al*, 1975; Van Putten and May, 1978). The response of the syndrome to anti-parkinsonian drugs is reported to be high (Rifkin, 1980). Therefore if some of the depressive episodes noted in schizophrenia (see Paper I) were in fact drug-induced akinesia they should improve with a drug such as orphenadrine. This idea was tested by a double-blind trial in chronic schizophrenic patients who complained of depression whilst in remission on regular depot neuroleptic drugs alone. Despite the claims for the existence of this syndrome no study has been attempted of the prevalence in an unselected sample of patients.

Method

The patients selected for the study were 40 Schneiderian or Feighner-positive chronic schizophrenic patients on depot neuroleptic injections received regularly at hospital. All had been on a stable dose for a minimum of three months in a maximum weekly equivalent of fluphenazine decanoate 12.5 mg or flupenthixol decanoate 20 mg. The only other drugs prescribed to these patients within the previous month were antiparkinsonian drugs or a benzodiazepine. All patients scored a minimum of 15 on the Beck Depressive Inventory (BDI: as for Study I) in the absence of overt morbidity from extrapyramidal symptoms, although minimal neurological symptoms might have been present on detailed physical examination (Johnson, 1978). All were free from any but the mildest positive schizophrenic symptoms and scored only five or less on the Brief Psychiatric Rating Scale where the score on the depression item was excluded.

On entering the trial any antiparkinsonian drug previously prescribed was discontinued, but nitrazepam was allowed in a maximum dose of 10 mg at night. The depot neuroleptic was continued in a constant dose for the duration of the trial.

During a washout period of one week all patients received a placebo tablet twice each day. At the beginning of the second week they were then randomly distributed to one of two groups, orphenadine, 50 mg twice daily or placebo, in identical tablets. At the end of a further four weeks both placebo and active drug were discontinued. Nitrazepam was continued if already being prescribed, but no other medication.

All patients were rated on the Hamilton Rating Scale for depression by the author at the end of the first week (placebo), fifth week (end of orphenadrine) and week nine.

Results

All patients were aged between 19–60 years (mean age 28.6 ± S.D. 8). Twenty-three patients were male, with an excess of three males in the placebo group, and one-third of the total were married. All patients had at least two previous acute episodes of schizophrenia and were on maintenance depot neuroleptic medication: flupenthixol 40 mg fortnightly (four cases) or three-weekly (10 cases) plus three patients on other regimes; or fluphenazine 25 mg fortnightly (eight cases) or three weekly (eight), plus seven on other regimes. The change of mood after four weeks on orphenadrine or placebo and the mood state after tablet discontinuation are shown in Table I. None of the differences reach levels of significance.

A detailed analysis of symptoms experienced by the patients showed only muscle weakness and muscle stiffness as subjective experience which significantly

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TABLE I

Mood change of schizophrenics on depot injections after four weeks of drug treatment

Patients	Orphenadrine group (N = 20)			Placebo group (N = 20)		
	N	Mean HRS	Relapse N	N	Mean HRS	Relapse N
No change or worse	7	–	–	11	—	–
Mild improvement	5	8	2	6	10.1	2
Good improvement	8	3.5	4	3	3.8	1

Mild improvement = improvement of more than 33 per cent of HRS (Hamilton) score, which remains greater than 5.
Relapse = number who did so by nine weeks.

($P < .05$) differentiated the orphenadrine and placebo patients who improved.

Discussion

The results show a high placebo response which makes it unlikely that levels of statistical significance could be achieved in relatively small samples. The difference between the orphenadrine and placebo response at the end of the first four weeks suggests that a proportion of patients may have been suffering from akinesia rather than true depression. It might have been expected that all true orphenadrine responders with akinesia would relapse when the drug was withdrawn, but the syndrome may vary spontaneously with time in any case. Also the dose of orphenadrine used was 50 mg b.d. and it might be argued that a higher dose would have produced a better response rate.

Any therapeutic effect of orephenadrine can be understood for one of three reasons. The addition of an antiparkinsonian drug may have relieved drug-induced extrapyramidal symptoms and relieved depression reactive or secondary to these symptoms. However the sample was carefully chosen to exclude patients with morbidity from extrapyramidal symptoms. A second reason is that orphenadrine may have either a true antidepressant effect or a mood-elevating action of its own. The pharmacological effects of the anticholinergic drugs are complex, and this possibility has not been fully explored. The third possibility is that orphenadrine has some other effect and has reversed a more subtle or less easily detected syndrome which the patient describes as depression. The fact that orphenadrine responders can be identified by symptoms of muscle origin when closely questioned must strongly support the possibility of this third alternative. At least 10–15 per cent of the total schizophrenic population with depression may be suffering from akinesia. This supports the conclusions of Klein and Davies (1969), Rifkin *et al* (1975) and Van Putten and May (1978) that a syndrome of akinetic depression does exist in drug-treated schizophrenics, and may be difficult to separate diagnostically from other forms of depression. If so, there may be therapeutic potential for antiparkinsonian drugs in selected patients but neither the overall response of depression in this study, nor the postulated frequency of the syndrome would justify the routine use of antiparkinsonian drugs with maintenance neuroleptic therapy.

IV. A Double-blind Trial of Nortriptyline for Depression in Chronic Schizophrenia

Summary: Fifty schizophrenic patients, maintained in remission and free from extrapyramidal signs on regular depot injections of neuroleptic, who developed an acute episode of depression, were treated for five weeks with nortriptyline or placebo blindly allotted. There was no significant difference in alleviation of depression. The nortriptyline treated patients developed more side-effects ($P < .05$). The mental state measured by the BPRS was similar for both groups at the start and throughout the trial.

It is a common clinical practice for schizophrenic patients on regular maintenance therapy who develop a depression to be prescribed an antidepressant drug in addition. This empirical practice has not been validated by adequate clinical trials (Siris *et al*, 1978). However it has often been noted that depression in

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the course of schizophrenia was less likely to respond favourably to antidepressant medications than other forms of depression, and sometimes the schizophrenic features were exacerbated by these drugs (Bennett *et al*, 1954; Goldman, 1958; Kuhn, 1958; Klein and Fink, 1962; Klein, 1965). This is not unexpected when the complex nature of depression in the course of drug-treated schizophrenia is considered, especially the neuroleptic-induced akinetic depression (Rifkin *et al*, 1975; Van Putten and May, 1978).

On the other hand various clinical reports have suggested that a combination of an antidepressant drug with a neuroleptic may be useful (Extein and Bowers, 1975; Freeman, 1967; Hedberg *et al*, 1971; Hanlon *et al*, 1964; Michaux *et al*, 1966; Piskin, 1972; Chouinard *et al*, 1975; Hedberg, 1971; Kurland *et al*, 1971; Hanlon *et al*, 1970). Prusoff *et al* (1979) in a double-blind trial in depressed patients explored the use of antidepressants in combination with perphenazine over six months. Their results were complicated, suggesting a reduction in depression only after four months on amitriptyline, but significantly more thought disorder. The study did not show any definite superiority of the amitriptyline-pherphenazine combination on symptomatic outcome or social functioning when compared to perphenazine alone. In a trial on acute schizodepressive psychoses patients prescribed amitriptyline in combination with chlorpromazine fared about as well as those on chlorpromazine alone (Brockington *et al*, 1978).

The present study is the first double-blind placebo controlled trial of a tricyclic antidepressant in the treatment of an acute depression in schizophrenic patients maintained in remission on regular depot neuroleptic injections.

Method

All were chronic schizophrenic patients, diagnosed on the basis of positive Feighner or Schneiderian symptoms, who met the criteria of depression described in Study I (BDI score of 15 or more). They were maintained in a steady mental state, free from extrapyramidal signs on either fluphenazine decanoate or flupenthixol decanoate in steady dose, as for Study III.

Patients were randomly distributed to either the active drug or placebo group. Depression was assessed at onset and end of the trial by the Hamilton Rating Scale. A side-effect check list was completed

TABLE I

Side effects in depressed chronic schizophrenics on depot neuroleptic

	Nortriptyline			Placebo		
	Onset	End	Change	Onset	End	Change
Dry mouth	12	21	+9	14	13	−1
Tremor	6	9	+3	8	10	+2
Constipation	1	7	+6	3	2	−1
Hypotension	0	2	+2	2	1	+1
Increased perspiration	3	6	+3	1	1	0
Tachycardia	2	3	+1	0	0	0
Diarrhoea	1	1	0	0	0	0
Blurred vision	11	14	+3	15	16	+1
Dizziness/weakness/faintness	2	7	+5	3	1	+2
Insomnia	3	2	−1	5	3	−1
Excitement	0	1	+1	1	1	0
Rigidity	1	5	+4	0	3	+3
Akathisia	2	4	+2	1	4	+3
Dystonia	0	0	0	0	0	0
Nausea or vomiting	0	0	0	0	0	0
Headache	0	2	+2	0	1	+1
Nasal congestion	2	3	+1	0	0	0
Weight gain	9	14	+5	14	15	+1
Drowsiness	4	7	+3	7	4	−3
Total side-effects			+49			+8
Total of patients complaining	14	23	+9	18	19	+1
Total of patients in group	25			25		

$P < .05$.

The scores are the numbers of people complaining of each symptom. Scores at onset of trial relate either to already continuing medication (neuroleptic, antiparkinsonian) or to the depression.

https://doi.org/10.1192/bjp.139.2.89 Published online by Cambridge University Press

on entry and thereafter weekly. The BPRS was completed at onset to ensure all patients with schizophrenic symptom activity (total score >5, excluding depression) were excluded; it was repeated at the end of the third and fifth weeks to detect patients whose schizophrenia had deteriorated significantly. Patients were also scored clinically on a simple four point scale to detect general deterioration, leading to increase in nortriptyline or to removal from the trial.

All patients were prescribed one tablet three times a day for two weeks. If no clinical improvement had taken place by the end of the second week the dose was increased to six tablets daily, unless the increase could not be tolerated. Each identical tablet contained either nortriptyline 25 mg or inactive placebo. The only other drugs allowed were the continuation of depot neuroleptic injections and oral antiparkinsonian drugs and benzodiazepines. The study was continued until 25 patients in each group completed a five week period of assessment.

Results

There were 23 men and 27 women aged 18–62 years (mean age 30.6 ± S.D. 9.4). All patients had had two or more admissions with schizophrenic breakdown. Two patients complained of side-effects on increasing their medication (nortriptyline) and it was reduced again to three tablets daily.

The nortriptyline group included an excess of two females but the two groups were similar in number of previous admissions (nortriptyline patients, mean 3.6 admissions; placebo mean, 3.2) and in HRS scores at onset (nortriptyline, mean 17.4; placebo, mean 16.1).

The nortriptyline-treated patients had significantly more side effects ($P < .05$) (Table I).

The change in depression is shown in Table II and failed to reach a level of significance.

TABLE II

Change in mood state after five weeks on nortriptyline or placebo

	Nortriptyline	Placebo
	N	N
Worse or no change	12	15
Improved (HRS down by 33% or more, but >5)	6	8
Good improvement (HRS score <5)	7	2
Total in group	25	25

Discussion

The same strong placebo response noted in the orphenadrine trial (Study III) was found here, with 40 per cent showing at least some improvement and this made it unlikely that a level of statistical difference could be reached in a small sample, although there were more in the nortriptyline group free of depression at the completion of the trial. If this trend had continued, a level of significance might well have been achieved. However, even so, it is important to emphasize that only a minority of the total of depressed patients would have responded. Thus there is nothing here to support the common practice of prescribing antidepressants to depressed schizophrenics and continuing such medication for lengthy periods in the absence of an early clinical response.

Acknowledgements

These studies were carried out between 1972–1980 in the North Manchester General Hospital and University Hospital of South Manchester. The author would like to thank his many colleagues who made these studies possible, particularly the nursing staff of the depot injection clinics, also Lundbeck Ltd who provided all drugs, placebo tablets and other materials for the double-blind trials.

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(*Received 18 August 1980; revised 19 January 1981*)