Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical outcome at one year

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Abstract

A study was conducted to investigate a novel approach to the prophylaxis of schizophrenic relapse. The treatment strategy comprised brief intermittent courses of neuroleptic agents begun as soon as non-psychotic symptoms believed to be early signs of relapse appeared. Fifty four stable, remitted outpatients meeting the American Psychiatric Association's DSM-III criteria for schizophrenia were randomised double blind to receive brief intermittent treatment with either active or placebo depot neuroleptic injections. Only three patients given placebo injections and two controls were admitted to hospital during one year of follow up. Eight (30%) of the patients given placebo injections and only 2 (7%) of the controls, however, had a recurrence of schizophrenic symptoms. Patients given placebo injections experienced fewer extrapyramidal side effects and showed a trend towards a reduction in tardive dyskinesia. Dysphoric and neurotic symptoms were identified before eight out of 11 relapses, and these symptoms were more frequent in patients given placebo depot injections.

These results suggest a viable but not necessarily better alternative to continuous oral or depot treatment for less ill, chronic, stabilised schizophrenics based on the early treatment of putative prodromal symptoms of relapse.

Introduction

The use of continuous neuroleptic treatment to prevent exacerbations of schizophrenic illness is virtually universal. Its efficacy is supported by a considerable weight of evidence from placebo controlled studies showing the superiority of neuroleptic treatment in preventing relapse.[1] Enthusiasm for continuous prophylaxis with neuroleptics, however, has been tempered in recent years by an increasing recognition of the risks, both actual and potential, of continuous drug exposure. The most alarming is the risk of tardive dyskinesia, which is estimated to occur in up to 41% of outpatients[2] and may be irreversible. The occurrence of distressing extrapyramidal side effects is also well recognised. The greasy masked facies, stooped posture, "dancing feet," and slow, shuffling gait mark some patients out in a crowd and have been linked to the occurrence of depressive and dysphoric symptoms,[3,4] impaired social functioning, and exacerbation of the negative symptoms of the illness.[6]

Recognition of these risks has prompted a search for alternative strategies of treatment designed to prevent or attenuate relapse while reducing drug exposure and side effects. One such strategy, first suggested by Herz and Melville, aims at identifying the earliest signs of decompensation with prompt but time limited treatment during such periods.[7] The strategy entails keeping patients drug free and regularly monitoring their clinical state and as such offers the opportunity for considerable reductions in drug exposure. An uncontrolled pilot investigation,[8] preliminary reports,[9-11] and a controlled study[12] have confirmed the feasibility of this approach.

The possibility of recognising signs suggestive of impending relapse is evidenced in Herz and Melville's retrospective study of the early signs of schizophrenic decompensation.[7] It is well recognised that depressive symptoms are a frequent accompaniment of schizophrenic illness[13,14] and it has been suggested that they form part of the process of decompensation, being more frequent at the onset of acute psychosis and subsiding in parallel with psychotic manifestations.[15,16] Herz and Melville, following up previous, mostly anecdotal or unsystematic reports reviewed by Docherty and colleagues,[17] found that such affective changes together with the emergence of other neurotic symptoms bore a potentially valuable temporal relation to the onset of relapse.[7]

In a retrospective study of 145 chronic schizophrenics and 80 family members Herz and Melville found that 102 of the patients and 74 of the family members noted mood changes and neurotic symptoms before the onset of relapse.[7] These symptoms were mostly of a non-specific type and not clearly related to the phenomena of psychosis. In more than half of the cases the duration of such symptoms, which they termed prodromal symptoms, was more than one week, after which relapse occurred. Herz and Melville argued that these prodromal symptoms represented the early stages of schizophrenic decompensation and hypothesised that the prompt introduction of neuroleptics at these stages would ameliorate prodromal symptoms and prevent subsequent progression to relapse. In a retrospective case note study of patients receiving early pharmacotherapeutic intervention for schizophrenic relapse, Heinrichs and colleagues reported that 24 of 38 patients evidenced insight into their illness in the early stages of decompensation. Of these, only two were admitted to hospital during relapse, the remainder being successfully restabilised as outpatients.[18]

HYPOTHESES

A strategy of prophylaxis based on intermittent neuroleptic treatment for early signs of relapse offers several potential benefits in comparison with the conventional strategy of continuous neuroleptic treatment. We expected that these would principally be derived from reduced exposure to neuroleptic agents and include a reduction in persistent side effects such as dyskinesia, akathisia, akinesia, and sedation. We further hypothesised that reduction in persistent side effects would lead to improvements in social functioning, and though we recognised that such a strategy would lead to an increase in the frequency of relapse, we reasoned that by prompt recognition and treatment

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of early signs such relapses could be attenuated to the point that their negative effects would be outweighed by the potential benefits of the new strategy. We expected our findings to accord with those found in so called "low dose" studies, in which reducing the dose of maintenance treatment to up to one tenth leads to an increase in the frequency of symptomatic exacerbations but no change in the frequency of serious relapse as evidenced by admission to hospital.[19 20]

This paper is a report of clinical outcome after one year in terms of symptoms, treatment, and side effects. Data on social outcome will be reported separately after a longer period of follow up.

Methods

SAMPLE

Fifty four patients meeting the American Psychiatric Association's DSM-III diagnostic criteria for schizophrenia[21] on the basis of case note examination were recruited into the study. Patients were additionally required to have been clinically stable for at least six months without florid psychotic symptoms (delusions, hallucinations, bizarre behaviour, or thought disorder) and to have been stabilised with a fixed dose of depot neuroleptic for at least two months. Patients in whom relapse had entailed definite risk to self or others in the past were excluded. Participating clinicians were requested to refer patients whom they thought might benefit from the brief intermittent treatment approach. Patients and, when possible, their nearest relative or cohabitee were interviewed separately and together and consent to the study obtained from both. Some 40% of patients referred were included in the study sample.

DESIGN

Patients were randomised into two groups. The control group (n=27) continued to receive fluphenazine decanoate in clinically optimal (that is, pretrial) doses, whereas in the intermittent treatment group (n=27) equivalent doses of placebo injections were substituted under double blind conditions.

Prodromal symptoms were defined on a clinical basis as the emergence of neurotic or dysphoric symptoms persisting for two days or more and causing noticeable distress to the patient. *Relapse* was defined as the re-emergence of florid psychotic symptoms such as delusions, hallucinations, bizarre behaviour, or thought disorder. A patient was also deemed to have relapsed if admission to hospital was required.

Each patient and his or her nearest relative or cohabitee (when possible) was given a one hour teaching session about schizophrenia and in particular about the early signs of relapse. These sessions were given in groups of six to 10 patients and were based on the educational material utilised by Leff and colleagues in their studies of family intervention in schizophrenia.[22] The material covered the aetiology, symptoms, treatment, and natural course of the illness. Patients were also instructed about prodromal symptoms of relapse and asked to identify any changes which they had noted before previous relapses. The importance of contacting the research team at the earliest sign of such developments was emphasised.

After beginning the trial patients were seen every four weeks alternately by a research psychiatrist and a community psychiatric nurse. It was necessary to be flexible for individual patients, depending on their clinical state, and additional visits were made to monitor patients who had relapsed, developed prodromal symptoms, failed to keep an appointment, or missed an injection. Patients were seen at least weekly during relapse and while prodromal symptoms were present. All patients had a 24 hour source of contact by telephone with the research psychiatrist or community psychiatric nurse.

Additional oral neuroleptic treatment was given to patients in both the intermittent treatment and control groups who developed prodromal symptoms or relapse. This was haloperidol, usually in the range 5-10 mg daily, though flexibility of dosage was allowed. Additional anticholinergic treatment was allowed if extrapyramidal side effects complicated the use of neuroleptic agents. All patients were given a starter pack of three days of oral treatment should they be unable to make contact with the research team at the earliest sign of decompensation.

A record of the number of interventions additional to those scheduled together with the dose, frequency, and reasons for giving additional treatment was kept for each patient. Dose of depot fluphenazine was converted to haloperidol equivalents on the basis of notional clinical equipotency of 1 mg fluphenazine decanoate intramuscularly and 2·62 mg haloperidol by mouth. This dose equivalence is supported by data on the relative clinical potency of these drugs derived from comparison of outcome in controlled trials and dose-response studies[23] but may overestimate the potency of the depot preparation as judged by relative plasma concentrations of active drug produced by a given dose.[24]

Treatment of prodromal symptoms continued for up to two weeks unless relapse occurred. Treatment of relapse was continued until four weeks after the remission of symptoms.

Patients were withdrawn from the double blind treatment and early intervention for prodromal symptoms if they (*a*) refused to comply with the treatment programme, (*b*) relapsed for a period of greater than eight weeks, or (*c*) relapsed on two or more occasions within six months. Patients withdrawn from double blind treatment were followed up under open treatment conditions until one year after the start of the trial and included in the analysis of outcome.

MEASURES

The *Manchester scale* is an eight item scale for rating psychotic symptoms on five points (0-4).[26] It consists of both positive and negative symptoms of schizophrenia. It was administered by the psychiatrist at baseline and thereafter every two months. It was also administered every two weeks during relapse.

The *global assessment scale* consists of 10 grades of psychopathology and overall functioning on a scale of 0-100.[26] It was administered together with the Manchester scale.

The *Herz early signs questionnaire* is the only scale specifically designed for rating the process of decompensation in schizophrenia.[8] The questionnaire is meant to assess patients' perceptions of themselves and consists of 32 questions rated on five points of severity (0=absent, 5=extreme). It was administered at baseline and every two months thereafter. It was also administered at the onset of prodromal symptoms and weekly for the subsequent two weeks.

The *symptom check list 90* is a self rating inventory consisting of 90 items relating to affective and neurotic symptoms and psychoses.[27] The amount of distress engendered by each symptom is rated on a four point scale (0-4). The scale was rated before entry into the trial and every four weeks thereafter, either during clinic attendance or at home during visits by the community psychiatric nurse. The scale was also filled out at the onset of prodromal symptoms and weekly for the subsequent two weeks.

The *extrapyramidal rating scale* is a modified Simpson-Angus rating scale.[28] The prevalence of global "non-liveliness," global parkinsonism, and specific extrapyramidal side effects was calculated by

collapsing down item scores into simple present-absent ratings. The scale was rated at baseline and at six month intervals.

The *abnormal involuntary movement scale* is an established rating scale used in the detection and treatment of tardive dyskinesia.[29] Tardive dyskinesia was rated as present if global severity of abnormal movement was rated as 2 or higher and was accompanied by a score of 2 or higher on any individual orofacial abnormal movement. The scale was rated at baseline and at six month intervals.

STATISTICS

Non-parametric tests of significance were used in all comparisons: they were the χ^2 test with Yates's correction and the Mann-Whitney U test for independent samples and Wilcoxon's signed rank test for non-independent samples. All tests were two tailed except in the comparison of relapse frequencies, where the expectation of greater relapse frequency in the control group was specifically discounted.

Results

BASELINE COMPARISONS AND DROPOUTS

Table I shows the baseline sociodemographic and clinical characteristics of the intermittent treatment and control groups. There was no significant difference between the groups in any baseline variable. The age at onset was slightly higher than might have been expected in an unselected sample and may reflect selection of a better prognostic group.

Six patients were withdrawn from double blind treatment in the intermittent treatment group and five in the control group. Table II gives the reasons. Of those patients withdrawn, five in each group had depot neuroleptic treatment re-established and one patient in the intermittent treatment group received no neuroleptic at all.

TABLE I—*Baseline characteristics of sample*

	Control group (n=27)	Intermittent treatment group (n=27)
Mean (SD) age (years)	42 (10)	41 (11)
No (%) female	14 (52)	17 (63)
No (%) living with relative or companion	18 (67)	17 (63)
Mean (SD) age at onset (years)	27 (10)	28 (9)
Mean (SD) duration of illness (years)	13 (8)	12 (9)
Mean (SD) No of previous admissions	3 (2)	3 (2)
No (%) in hospital for six months	8 (30)	9 (33)
No (%) ill within previous year	4 (15)	7 (26)
Mean (SD) monthly fluphenazine decanoate dose over previous two months (mg)	28·2 (16·5)	29·6 (17·7)
Mean (SD) Manchester scale score	2·0 (2·1)	1·3 (1·4)
Mean (SD) global assessment scale score	73 (13)	78 (11)

TABLE II—*Numbers of patients withdrawn from double blind treatment*

Reason for withdrawal	Control group (n=27)	Intermittent treatment group (n=27)
Refused to comply	4	2
Ill more than eight weeks	1	3
Two or more relapses in six months	0	1
Total	5	6

RELAPSE RATES AND ONE YEAR FOLLOW UP

Table III shows the outcome in all patients who were entered into the study. Relapse was significantly more frequent in the intermittent treatment group (eight patients) than in the controls (two), but this difference was not accompanied by any significant increase in the frequency of admission to hospital in the intermittent treatment group. In both groups the rate of admission was low (five patients), and high minimal global assessment scale scores during relapses and infrequent use of compulsory powers indicate that severe relapse was uncommon. Prodromal symptoms were identified prospectively (that is, before relapse) in eight of the 11 relapses.

Despite the increased rate of recurrence of psychotic symptoms in the intermittent treatment group there was no overall difference between this group (n=27) and the controls (n=27) in the regular bimonthly ratings of psychotic symptoms. Mean score on the Manchester scale did not differ significantly between the groups at baseline (table I), and mean group scores obtained bimonthly throughout the trial and compared at each time point failed to yield significant differences between the intermittent treatment group (median 1·4, range 0·9-2·0) and the controls (median 1·9, range 1·7-2·2) at any stage in the study (Mann-Whitney U tests). Parallel findings were obtained for global assessments of psychopathology and social functioning. Mean global assessment scale scores (table I) did not differ significantly between groups at baseline and ranged from 71 to 77 in controls (median 74) and from 75 to 80 in the intermittent treatment group (median 78) with no significant difference between groups at any bimonthly assessment (Mann-Whitney U tests).

When all treatment was taken into account, including that given to patients withdrawn early from double blind treatment and followed up openly, the intermittent treatment group, as predicted, received significantly less total treatment (haloperidol equivalents) than controls (table III).

PRODROMAL EPISODES

Table IV shows the outcome in patients who completed one year of double blind treatment and early intervention for prodromal symptoms. Significantly more patients experienced prodromal symptoms in the intermittent treatment group (16/21; 76%) than in the control group (6/22; 27%). The intermittent treatment group as a whole also received significantly more

TABLE III—*Outcome in all patients*

	Control group (n=27)	Intermittent treatment group (n=27)	Significance of difference between groups
No (%) relapsed	2 (7)	8 (30)	χ^2=3·0682; df=1; 1 tailed p=0·0399; 90% confidence interval of difference 2% to 43%
No of relapses	2	9	—
No of prodromal symptoms identified before relapse	2	6	—
Median (range) duration of relapse (days)	51 (11-90) (n=2)	32 (4-75) (n=8)	NS
Median (range) minimal global assessment scale score during relapse	39 (22-51) (n=2)	40 (25-60) (n=8)	NS
Total No of admissions	2	3	NS
Median (range) duration of hospital stay (days)	41 (5-77) (n=2)	28 (4-57) (n=3)	NS
No for whom compulsory powers of admission were used	0	1	NS
Mean (SD) total neuroleptic dose (haloperidol equivalents, mg*)	1019 (837)	362 (513)	Mann-Whitney U test=103·0; 2 tailed p<0·0001

*Based on dose equivalence of 1 mg fluphenazine decanoate intramuscularly and 2·62 mg haloperidol by mouth.

non-specific management in the form of supportive interventions by the psychiatrist or community psychiatric nurse. A total of 44 prodromal episodes, as operationally defined, were recorded in the whole study sample. Of these, eight occurred before relapses, the remaining 36 being isolated phenomena bearing no clear relation to relapse. As in the whole study sample, the intermittent treatment group received less total neuroleptic treatment despite more frequent use of oral haloperidol (table IV).

Table V shows the symptom check list 90 subscale scores before, during, and after the 44 prodromal episodes. Significant increases in subscale scores for depression, anxiety, phobic anxiety, obsessionality, and interpersonal sensitivity together with significant increases in scores for psychosis, paranoid symptoms, and global severity of distress occurred at the onset of prodromal symptoms compared with routine assessments within one month of the onset of prodromal symptoms. Scores on these scales reverted to values not significantly higher than those at baseline after two weeks of neuroleptic treatment (Wilcoxon matched pairs signed rank tests).

Individual item scores on the Herz early signs questionnaire obtained at the onset of prodromal symptoms were compared with those obtained at routine assessment conducted within two months of onset of each prodromal episode in order to characterise symptoms emergent at the onset of the episodes. As before, a pattern of emergence of a broad range of non-specific symptoms that could be regarded as dysphoric was observed. Table VI outlines the frequencies of these emergent symptoms.

TABLE VI—*Frequency of emergent symptoms at onset of prodromal episodes (Herz early signs questionnaire)*

Emergent symptom	No (%) of prodromal episodes (n=44)
Fear of going "crazy"	31 (70)
Loss of interest	29 (66)
Discouragement about future	27 (61)
Labile mood	25 (57)
Reduced attention and concentration	25 (57)
Preoccupation with one or two things	22 (50)
Feelings of not fitting in	21 (48)
Fear of future adversity	21 (48)
Overwhelmed by demands	21 (48)
Loss of interest in dress/appearance	20 (45)
Reduced energy	19 (43)
Puzzled/confused about experience	18 (41)
Loss of control	18 (41)
Boredom	18 (41)
Thoughts racing	18 (41)
Indecisiveness	18 (41)
Distanced from friends/family	15 (34)
Feeling that others don't understand	15 (34)
Disturbing dreams	14 (32)
Loneliness	14 (32)
Reduced sex drive	12 (27)
Fear of being alone	12 (27)
Increased energy	10 (23)
Increased perceptual intensity	8 (18)
Increased sex drive	7 (16)
Depersonalisation	6 (14)
Religious preoccupation	5 (11)
Ideas of reference	3 (7)
Elevated mood	2 (5)
Risk taking	2 (5)

MOVEMENT DISORDER

Table VII shows the point prevalence of extrapyramidal side effects for both the intermittent treatment and control groups. At baseline controls had a greater prevalence of extrapyramidal side effects. These differences, however, did not achieve statistical significance. At both six and 12 months of follow up akathisia and non-liveliness were significantly less prevalent in the intermittent treatment group. At 12 months of follow up these patients also had a significantly lower prevalence of gait abnormality and global parkinsonism.

In order to obtain an overall rating of extrapyramidal side effects scores on individual items of the extrapyramidal rating scale were summed to produce a total extrapyramidal symptom score for each patient (table VIII). At baseline there was no difference between groups on this measure. At both six months and one year, however, total symptom scores were significantly lower in the intermittent treatment group.

Table IX shows the point prevalence data for tardive dyskinesia. At baseline there was no difference between the groups. Point prevalence rose in the controls and remained comparatively stable in the intermittent treatment group in the one year follow up period. At one year the difference between the groups approached statistical significance (p=0·08), indicating a trend towards a lower prevalence in patients given intermittent treatment than in controls.

TABLE IV—*Outcome in patients completing double blind treatment*

	Control group (n=22)	Intermittent treatment group (n=21)	Significance of difference between groups
No (%) with prodromal episodes	6 (27)	16 (76)	χ^2=9·7862; df=1; 2 tailed p=0·0018; 95% confidence interval of difference 18% to 80%
Mean (SD) monthly dose of depot fluphenazine per patient (mg)	25·6 (9·0)	0	
Total oral haloperidol dose in group (mg)	1408	3444	
Mean (SD) total neuroleptic dose (haloperidol equivalents, mg*)	868 (354)	164 (190)	Mann-Whitney U test=6·0; 2 tailed p<0·0001
Total No of interventions additional to those scheduled	28	96	Mann-Whitney U test=98·0; 2 tailed p=0·0007

*Based on dose equivalence of 1 mg fluphenazine decanoate intramuscularly and 2·62 mg haloperidol by mouth.

TABLE V—*Mean item scores on symptom check list 90 subscales at routine assessment immediately before onset of prodromal episode, at onset of episode, and two weeks after onset of 44 prodromal episodes*

Subscale	Mean item scores: Before onset (within one month)	Mean item scores: Onset	Mean item scores: Two weeks after onset	Significance of difference between onset and preonset scores (Wilcoxon matched pairs signed rank test)
Global severity	0·567	0·898	0·575	p=0·0060; Z=−3·4544
Somatisation	0·413	0·696	0·467	p=0·0454; Z=−2·0008
Depression	0·791	1·223	0·745	p=0·0021; Z=−3·0793
Anxiety	0·514	0·924	0·600	p=0·0016; Z=−3·1530
Phobic anxiety	0·374	0·735	0·502	p=0·0158; Z=−2·4138
Obsessive-compulsive	0·593	0·995	0·568	p=0·0006; Z=−3·4535
Psychoticism	0·505	0·750	0·522	p=0·0054; Z=−2·7808
Paranoid	0·631	0·992	0·585	p=0·0036; Z=−2·9070
Hostility	0·460	0·401	0·452	NS
Interpersonal	0·812	1·116	0·834	p=0·0050; Z=−2·8038

Discussion

CLINICAL FINDINGS

Brief intermittent treatment was associated with a significantly higher rate of episodes of both psychotic and dysphoric-neurotic symptoms when compared with continuous neuroleptic treatment. This is consistent with findings well established in other reports.[1]

TABLE VII—*Point prevalence of extrapyramidal side effects. Figures are numbers (percentages) of patients*

	Control group (n=22)	Intermittent treatment group (n=21)	Significance of difference between groups
Hypomimia:			
Baseline	9 (41)	5 (24)	NS
6 Months	8 (36)	2 (10)	NS
1 Year	6 (27)	1 (5)	NS
Rigidity:			
Baseline	3 (14)	4 (19)	NS
6 Months	1 (5)	0	NS
1 Year	5 (23)	2 (10)	NS
Tremor:			
Baseline	6 (27)	5 (24)	NS
6 Months	4 (18)	1 (5)	NS
1 Year	5 (23)	1 (5)	NS
Akathisia:			
Baseline	10 (45)	7 (33)	NS
6 Months	6 (27)	0	χ^2=4·0874; df=1; 2 tailed p=0·0432
1 Year	11 (50)	2 (10)	χ^2=6·5367; df=1; 2 tailed p=0·0106
Gait abnormality:			
Baseline	8 (36)	5 (24)	NS
6 Months	7 (32)	1 (5)	NS
1 Year	6 (27)	0	χ^2=4·0874; df=1; 2 tailed p=0·0432
Global parkinsonism:			
Baseline	11 (50)	7 (33)	NS
6 Months	6 (27)	2 (10)	NS
1 Year	8 (36)	1 (5)	χ^2=4·7155; df=1; 2 tailed p=0·0299
Global non-liveliness:			
Baseline	15 (68)	9 (43)	NS
6 Months	13 (59)	3 (14)	χ^2=7·4136; df=1; 2 tailed p=0·0065
1 Year	12 (55)	1 (5)	χ^2=10·3747; df=1; 2 tailed p=0·0013

TABLE VIII—*Mean total extrapyramidal side effect scores (SD in parentheses)*

	Control group (n=22)	Intermittent treatment group (n=21)	Significance of difference between groups
Baseline	3·9 (3·1)	2·3 (2·6)	NS
6 Months	2·8 (2·7)	0·5 (1·4)	Mann-Whitney U test=118·5; 2 tailed p=0·0026
1 Year	3·2 (3·0)	0·4 (1·2)	Mann-Whitney U test=99·5; 2 tailed p=0·0004

TABLE IX—*Point prevalence of tardive dyskinesia. Figures are numbers (percentages) of patients*

	Control group (n=22)	Intermittent treatment group (n=21)	Significance of difference between groups
Baseline	7 (32)	6 (29)	χ^2=0·0; df=1; 2 tailed p=1·0000
6 Months	9 (41)	7 (33)	χ^2=0·0393; df=1; 2 tailed p=0·8429
1 Year	12 (55)	5 (24)	χ^2=3·0578; df=1; 2 tailed p=0·0804; 95% confidence interval of difference −2% to 63%

Such events, however, were in most cases considerably less dramatic than relapse as generally conceived in clinical practice. Global assessment scale scores during relapse showed a comparatively mild level of disturbance in most cases and only one patient required compulsory admission. The frequency of admission to hospital was low (5/54 patients) and the higher rate of relapse in the intermittent treatment group was not paralleled by a significantly greater frequency of admission. Brief intermittent treatment therefore appears to attenuate such relapses as do occur but at the expense of more frequent episodes of clinical disturbance. Though not as effective in preventing psychotic symptoms, it has the advantages of reduced exposure to drugs and fewer extrapyramidal side effects.

Our findings also suggest that brief intermittent treatment is associated with a reduced risk of tardive dyskinesia. Though exposure to neuroleptic agents is recognised as an important risk factor for tardive dyskinesia,[30] there is an increasingly held view that the disorder may in part represent an intrinsic component of the schizophrenic disease process, being found with greater than expected prevalence in patients not exposed to neuroleptics.[31] Other studies have produced conflicting evidence on the relation between tardive dyskinesia and both dosage and duration of neuroleptic treatment.[32] Indeed some reports have suggested a greater risk of persistent tardive dyskinesia with intermittent treatment than with continuous treatment.[33,34] Care should therefore be exercised in interpreting the trends in the prevalence of tardive dyskinesia found in this investigation after only one year. Larger numbers of patients followed up for a longer period are required in order to characterise the effects of intermittent treatment on this condition.

Patients allocated to receive brief intermittent treatment alone had almost two thirds less drug over one year than controls, even when taking into account treatment in those patients withdrawn prematurely from double blind treatment because of refusal to comply or because of prolonged (over eight weeks) or frequent (two or more episodes in six months) relapse. This finding supports the results of a recent open investigation of intermittent treatment for early decompensation in which exposure to treatment over two years was found to be less than two thirds that of controls receiving continuous treatment.[1,2] A study of 60 chronic schizophrenics withdrawn from maintenance neuroleptic agents in a conventional treatment setting found that exposure to these agents was one third greater in patients who stopped maintenance treatment than in matched controls who continued with neuroleptics over 18 months.[35] This finding also held for a subgroup who discontinued treatment on the advice of their psychiatrist in view of an expected good prognosis. The better results in the intermittent treatment studies that attempt to recognise and treat early decompensation add further weight to the argument that early intervention is successful in attenuating relapse.

Our findings indirectly support those of a recent two year follow up study of maintenance treatment with low and conventional doses in stabilised schizophrenic outpatients.[20] Patients in that study were randomly assigned to receive standard (25 mg/two weeks) or low (5 mg/two weeks) maintenance doses of fluphenazine decanoate. A substantially lower relapse rate (36%) was seen in the group given the standard dose when compared with the low dose group (69%). Nevertheless, when clinicians were permitted to make a dosage adjustment at the earliest sign of psychotic exacerbation there was no difference in relapse rates between standard and low dose groups.

The number of relapses in our study was small (11), and multiple tests of statistical significance employed in the analysis of outcome increase the chance likelihood of positive findings. Care must therefore be taken to avoid making firm conclusions. Our patients were a selected group of remitted schizophrenics with a good prognosis, and the findings should not be generalised to the disorder as a whole. Also long acting depot agents are known to persist in body fluids for many months after stopping treatment.[36] Possibly such medication may have contributed to both a lower relapse rate and a lessened severity of relapse than otherwise expected in patients withdrawn from continuous depot treatment.

This study suggests that a strategy of intermittent treatment for early signs of schizophrenic decompensation may be a useful alternative to continuous drug treatment. For the cooperative patient with adequate insight the brief intermittent treatment strategy is less effective than continuous drug treatment in preventing the recurrence of symptoms but is as effective in preventing severe relapse and also minimises exposure to neuroleptic drugs and side effects. The approach may prove an acceptable alternative in otherwise cooperative patients who wish to stop prophylactic treatment or are suffering from incipient or established tardive dyskinesia, severe weight gain, or disabling extrapyramidal side effects.

The overall social effects of the brief intermittent treatment approach and the outcome after longer

follow up are still under study and will be reported later.

COST EFFECTIVENESS COMPARISONS

The brief intermittent treatment strategy is more demanding of medical and nursing manpower than conventional continuous neuroleptic treatment. The amount of non-specific treatment in the form of supportive interventions by the psychiatrist and community psychiatric nurse was significantly greater within the brief intermittent treatment group than in patients receiving continuous neuroleptic treatment. This is not surprising, as such non-specific treatment was for the most part contingent on noting the development of prodromal symptoms or relapse. The educational component of the study, however, was limited to a single group session and we did not employ the intensive weekly group follow up utilised to monitor progress in other studies of early detection and treatment.[12] The research psychiatrist and community psychiatric nurse were responsible for the clinical management of over 90 schizophrenic patients in the community during the study, including the 54 patients reported on in this paper who required detailed research evaluation. Our impression is that the additional non-specific treatment required in the brief intermittent treatment approach is not of such magnitude as to preclude use of the strategy in the normal clinical setting.

RELEVANCE OF PRODROMAL EPISODES

The theoretical rationale for a programme of treatment based on the early detection and treatment of prodromal symptoms is supported by the finding that eight out of 11 relapses were preceded by such symptoms. This finding is consistent with a previous retrospective study[7] and attests to the feasibility of detecting and treating early signs of schizophrenic relapse.

The pattern of dysphoric and neurotic symptoms reported in prodromal episodes was not specific for schizophrenia. The exception to this finding was the frequent report of the fear of "going crazy" in our study, possibly because patients were trained to recognise the emergence of neurotic and dysphoric symptoms as indicating a relapse of their illness.

We emphasise that altogether some 44 prodromal episodes were recorded, of which 36 were isolated phenomena bearing no clear relation to relapse. The greater frequency of such episodes when patients were between treatments suggests that they may form part of the process of schizophrenic decompensation, in abeyance under the influence of neuroleptics. All our patients, however, were given oral haloperidol when these symptoms occurred. Because dysphoria is a common response to adverse life events and chronic difficulties which occur independently of illness, only a controlled study in which a random sample of prodromal episodes is blindly treated with neuroleptic or placebo would tell us if relapse would have followed these isolated prodromal episodes without treatment.

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