Long-term morbidity associated with delayed treatment of first admission schizophrenic patients: a re-analysis of the Camarillo State Hospital data

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ABSTRACT

Background. The authors examined data from a follow-up study of first admission schizophrenic patients treated with and without antipsychotic medications, who were discharged from the hospital within 6 months. It was predicted that patients who did not require antipsychotic medications for discharge would have a more favourable long-term outcome.

Methods. The subjects were part of the Camarillo State Hospital study conducted by May and colleagues in the late 1950s and early 1960s. Patients had been randomly assigned to treatment with and without antipsychotic medications. The number of rehospitalization days and total prescribed chlorpromazine equivalents were calculated for each patient for the 2 years following discharge. In order to assess patients' continuing ability to function, 11 patients from each group who met DSM-IV criteria for schizophrenia were matched for age, educational status at first admission, race, and gender; their Global Assessment of Functioning Scale (GAF) score was estimated across a period of 6–7 years following discharge.

Results. During the second year following discharge, patients initially treated with antipsychotic medications required fewer rehospitalization days than the initially non-medicated patients. Furthermore, 6–7 years following initial discharge, those patients initially treated with medications were functioning at a higher level, as measured by GAF scores, than patients not initially treated with antipsychotic medications.

Conclusions. The results of this study suggest that, at least for this subgroup of patients, early treatment with antipsychotic medications both decreases the immediate morbidity associated with schizophrenia, and prevents detrimental changes possibly related to prolonged untreated psychosis.

INTRODUCTION

When antipsychotic medications were introduced in the mid-1950s, there was optimism that their short-term administration would produce long-term benefits. Yet studies done at that time seemed to demonstrate that the optimism was not justified; the majority of schizophrenic patients initially treated with antipsychotic medications relapsed and required subsequent rehospitalization. It was not long before it became clear that most patients with schizophrenia require maintenance treatment with antipsychotic medications, although even today just how long that treatment should continue has not been empirically determined (Gilbert *et al.* 1995; Wyatt, 1995*a*).

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The potential long-term benefits of early treatment with antipsychotic medications for schizophrenia have again surfaced with the publication of several recent studies (Crow et al. 1986; McEvoy et al. 1991; Loebel et al. 1992; Waddington et al. 1995), together with some theoretical and data-based reviews of the subject (Davis & Chang, 1978; David & Andrivkatis, 1986; Miller, 1989; Wyatt, 1991, 1995b). These reports suggest that early intervention with antipsychotic medications does affect the long-term course of schizophrenia. One of the most compelling studies demonstrating this effect was performed by May and colleagues (May, 1968; May et al. 1976a, b, 1981) during the late 1950s and early 1960s. Patients experiencing their first hospitalization for schizophrenia were randomly assigned to one of five treatment groups: milieu therapy alone, psychotherapy alone, ECT, antipsychotic medications, and antipsychotic medications plus psychotherapy. Those patients given either ECT or antipsychotic medications with, or without, psychotherapy had shorter initial hospitalizations than patients who were not given ECT or antipsychotic medications. At regular intervals for up to 5 years following their discharge, the status of these patients was examined. While most patients did poorly, the patients who did the best tended to be those who were given either ECT or antipsychotic medications during their initial hospitalization.

In spite of the results from the study by May and colleagues, as well as other studies that indicate that early treatment with antipsychotic medications decreases the morbidity of schizophrenia, there appears to be a subgroup of schizophrenic patients for whom treatment with antipsychotic medications (or ECT) may not be necessary (Carpenter et al. 1977). One might expect that these good outcome patients would not require treatment with antipsychotic medications during their initial hospitalization. To explore this possibility, we compared the outcome of those patients in the study by May and colleagues who were treated with antipsychotic medications (with or without psychotherapy) with those patients who received milieu therapy or psychotherapy alone; all patients had been discharged within 6 months of admission. We chose 6 months as a cut-off point because, even with today's improved treatments, first admission schizophrenic patients typically require

a mean of 35·7 weeks to return to baseline (Lieberman et al. 1993). Furthermore, in the study by May and colleagues, patients who had not sufficiently improved within 6 months, or whose therapist/supervisor thought the patients had less than a one in ten chance of being discharged within the next 6 months, usually had their treatment changed to antipsychotic medication plus group psychotherapy (Tuma & May, 1979).

The hypothesis that led to the present study was that patients who did not receive antipsychotic medications, but were nevertheless capable of being discharged within 6 months, would do better during follow-up than those patients who received antipsychotic medications and probably would not have been discharged without them.

METHOD

Subjects

Patient selection in the original May et al. (1968) *study*

Patients between the ages of 16 and 45 who were having their first 'significant' hospital admission were studied. The patients had no evidence of organic brain damage, epilepsy, or major physical illness. Other exclusion criteria included: more than 31 days in any one hospital or 45 days in a combination of hospitals, and any somatic therapies unless they totalled less than 21 continuous days of antipsychotic medication. The discharge date was defined as the date the patient first left the hospital, provided he, or she, remained out of the hospital for more than 21 days.

Six thousand nine hundred patients with a hospital diagnosis of schizophrenia were screened between 18 June 1959 and 19 December 1962. Two hundred and forty-seven patients were accepted into the study, and 228 completed it. The present analysis combines the psychotherapy and milieu groups into one group, called the initially non-medicated group, and the antipsychotic medication and psychotherapy plus antipsychotic medication groups into a second one, called the initially medicated group. This report does not analyse data from patients in the ECT group. Also, because of the nature of the treatments and the era when May and

colleagues carried out their study, the study was not performed 'blind'.

It is important to note that, once patients were released from the hospital, they were no longer part of the formal experiment and were treated as thought best by their physicians, and according to their own wishes. For this reason, then, the terms 'initially non-medicated' and 'initially medicated', refer to the patients' initial hospital experimental treatment, not the treatment they received after they were discharged from the hospital.

Patient selection – present study

Study One – days of rehospitalization for patients followed at least 2 years

Patients in the initially non-medicated (psychotherapy and milieu therapy) and initially medicated groups (antipsychotic medication and psychotherapy plus antipsychotic medication) who were discharged within 6 months of admission were candidates for the present study. Out of a starting total of 89 patients in the initially non-medicated group, and 92 in the initially medicated group, 25 (28·1%) and 71 (77·2%), respectively, were released within 6 months of hospitalization ($\chi^2 = 43·7$, $P < 0·0001$).

Unfortunately, we were able to locate data on only a limited number of variables from the study by May and colleagues (1968). For almost all patients, however, data on race, gender, educational level, age at first admission, marital status, and length of first hospitalization were available from preserved records. For the patients who were discharged within 6 months, information regarding the number of days of rehospitalization during the 2 years of follow-up, as well as the amount and type of antipsychotic medications the patients received during this period (usually trifluoperazine or chlorpromazine, which were converted into chlorpromazine equivalents (Jeste & Wyatt, 1982)) was available. Most of the patients in the original study by May and colleagues were followed for longer than 2 years, but the number of retrievable records for the initially non-medicated patients dropped to about 55% after the second year, so we chose to analyse data for the first 2 years only.

Study Two – measure of function in matched subgroups

No formal measures of function from the study by May and colleagues could be located, and the Camarillo State Hospital charts had been thinned of all but the most rudimentary information. We were however, able to locate abbreviated hospital charts for 11 of the patients in the initially non-medicated group. These 11 charts, as well as the 53 hospital charts available from patients in the initially medicated group, were examined for information which might identify the experimental group to which the patients had been assigned; that information, however, was eliminated from the charts. The 11 patients in the initially non-medicated group were matched by race, gender, educational level and age at first hospital admission with similar patients from the initially medicated group by a research assistant who was unaware of the nature of the study. These 22 charts were reviewed blindly to ensure that all patients met DSM-IV criteria for schizophrenia (APA, 1994). Four raters who were blind to the initial medication status of the patients rated the charts using the Global Assessment of Functioning Scale (GAF) (APA, 1987). The raters included two master's level and two doctoral level psychologists. The raters were instructed to give each subject a GAF score based on a global impression of the information in each chart. They received no special instruction on how to weigh the various aspects of function, or on how to 'blend' ratings across the length of the follow-up period. Interrater reliability (ICC) for the four raters (Bartko, 1976) was 0·81.

Data analysis

The results are reported as mean ± S.D. Because the sample sizes were uneven, variances were often unequal, and there were many ties in the data (for example, zero days rehospitalization), group comparisons in Study One were made with nonparametric statistics using chi-square and Wilcoxon–Mann–Whitney tests. In Study Two, comparisons between groups were made with paired t tests. All tests were two-tailed and values of $P \leqslant 0·05$ were considered significant.

RESULTS

Study One – days of rehospitalization during 2 year follow-up

There were no significant differences at first admission for age, educational level, gender, marital status or racial make-up between the two groups (Table 1). There was no difference in rehospitalization days for year one, but for year two the initially non-medicated patients required more rehospitalization days ($P = 0.01$). The initially medicated patients were given more medication in chlorpromazine equivalents during year one ($P = 0.0002$), but not during year two.

To explore the possibility that the difference in the amount of antipsychotic medication received in year one could account for the difference in rehospitalization days during year two, a group matching technique ('nearest mean adjustment analysis') was used to equate roughly the groups for the amount of antipsychotic medications taken during year one. Patients from the initially medicated group were successively dropped by descending rank order until the least distance was found between the means (in other words, the means were closest)

of chlorpromazine equivalents for the initially medicated and initially non-medicated groups in year one. The means were closest after 24 patients had been excluded from the initially medicated group (Table 1). After excluding these 24 patients, the difference in rehospitalization days for year two remained statistically significant ($P = 0.03$). This group matching technique also found that, for year one, the number of rehospitalization days was two-fold greater for the initially non-medicated patients; however, this difference was not statistically significant ($P = 0.21$).

Study Two – measure of function in matched subgroups

The groups were matched for race, educational level, and gender (Table 2). Although they were not matched for marital status at admission (six patients in the initially non-medicated group and five patients in the initially medicated group had never been married), or the number of days of first hospitalization (non-medicated 129.5 ± 31.7; medicated 114.6 ± 37.7), the groups were roughly comparable. There was, however, a statistically significant difference between the GAF scores for the two groups. Higher scores,

Table 1. *Demographics and outcome variables for patients in the initially non-medicated and initially medicated groups who were discharged from the hospital within 6 months of their first admission*

Patient group	Initially non-medicated	Initially medicated		Nearest mean adjustment analysis: initially medicated	
N	25	71		57	
Age at first admission	29.2 ± 8.86	29.0 ± 6.18	NS		
Gender (%)			NS		
Male	52	42			
Female	48	58			
Race (%)*			NS		
Caucasian	72.0	71.4			
African American	16.0	21.4			
Hispanic	12.0	5.7			
Oriental	0	1.4			
Marital status (%)*			NS		
Ever married	60	73			
Never married	40	27			
Highest grade attained*	11.8 ± 2.1	11.8 ± 2.0			
Rehospitalization days					
Year 1	30.1 ± 51.2	21.2 ± 48.3	NS	15.3 ± 36.3	NS
Year 2	74.8 ± 101.7	34.1 ± 67.9	$P = 0.01$†	36.1 ± 68.1	$P = 0.03$†
CPZ Equivalents/year (daily CPZ equivalents)					
Year 1	$57\,276 \pm 111\,284$ (157)	$92\,306 \pm 99\,338$ (253)	$P = 0.0002$	$55\,466 \pm 42\,154$	NS
Year 2	$72\,252 \pm 97\,163$ (198)	$73\,797 \pm 103\,482$ (193)	NS	$58\,680 \pm 91\,649$	$P = 0.03$†

* Information about race, highest grade attended and marital status was not available for all patients.
† Wilcoxon–Mann–Whitney test; NS, not significant.

Table 2. *Patient characteristics for patients initially treated without and with antipsychotic medication*

Non-medicated patients				Medicated patients			
Race	Education (yr)	Gender	Age at hospitalization	Race	Education (yr)	Gender	Age at hospitalization
CAU	10	M	33	CAU	11	M	32
CAU	10	M	16	HIS	9	M	20
CAU	12	F	37	CAU	12	F	36
AA	12	M	25	AA	12	M	23
CAU	14	F	34	CAU	14	F	32
HIS	16	M	29	CAU	16	M	29
CAU	13	M	22	CAU	12	M	22
CAU	9	F	44	CAU	9	F	39
CAU	12	M	32	CAU	12	M	35
CAU	12	F	19	CAU	12	F	25
CAU	11	M	19	CAU	11	M	18
Mean	11·8	7M, 4F	28·2		11·8	7M, 4F	28·3
S.D.	2·3		8·7		2·0		7·0

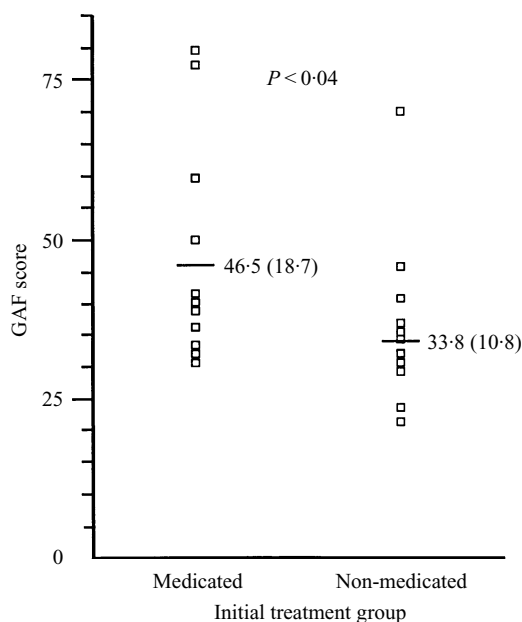CAU = Caucasian; AA = Afro-American; HIS = Hispanic.

FIG. 1. Global Assessment of Functioning Scale (GAF) scores 6–7 years after discharge for 11 initially medicated patients meeting DSM-IV criteria for schizophrenia, closely matched with 11 patients initially not treated with antipsychotic medications. Patients were matched for age, educational level at first admission, race, and gender. All patients were discharged from the hospital within 6 months of their first admission. Statistics: paired two-tailed t test.

which reflect better functioning ($t = 2·38$, $P = 0·038$, see Fig. 1), were obtained by the initially medicated group. The length of follow-up was comparable for the two groups (initially non-medicated ($72·6 \pm 52·7$) and medicated ($88·4 \pm 69·0$)), and does not explain the difference in GAF scores.

DISCUSSION

Patients with schizophrenia who were not treated with antipsychotic medications during their first admission, and who were sufficiently stable to be discharged within 6 months, were doing worse at follow-up than patients who had initially been treated with antipsychotic medications and also released within 6 months. The initially non-medicated patients required more days of rehospitalization during the second year of follow-up, and, across a period of 6–7 years, were not functioning as well. The discussion which follows deals with the limitations of this study, and considers what, if any, generalizations for clinical practice can be made from these findings to other groups of schizophrenic patients.

Size of patient sample

While the three-fold difference in response rate during the experimental period is indicative of the slow recovery associated with not treating first admission schizophrenic patients with antipsychotic medications, the relatively small number of better response patients who were able to leave the hospital within 6 months, particularly in the initially non-medicated group,

limits the degree to which the present results can be generalized to other groups of patients. Nevertheless, the results are valuable because it seems unlikely that future studies will be able to examine first admission schizophrenic patients randomly assigned to treatment without antipsychotic medications.

Use of rehospitalization days as an outcome measure

The use of rehospitalization days has several advantages over traditional behaviour ratings of symptoms. The number of hospitalization days is an objective measure of many, often subjective, observations. It usually involves the integrated judgement of several individuals, including the patient, his or her family, the community, mental health professionals and, at times, the judicial system. Also, if the sampling is complete, as it was for the patients in this study, it requires no statistical estimate of reliability.

Using the GAF as an outcome measure of function

Because of the dearth of information available we found it necessary to use a global rating of the patients' level of function. The GAF is a multidimensional measure which requires raters to integrate subjectively psychological, social, and occupational functioning on a hypothetical continuum of mental health illness into one score. Despite the complexity of the judgement that goes into making the ratings, we obtained high inter-rater reliability. GAF scores below 50 are considered to be associated with serious psychosocial impairment. In the present study, where knowledge of patients' specific symptoms was not available, low GAF scores indicate that patients had serious impairment in social and/or occupational functioning.

Interpreting the effects of maintenance medications on long-term outcome

Since psychiatrists and patients are likely to continue what seems to have worked, patients stable enough to be discharged from the hospital without antipsychotic medications, who were treated only with psycho- or milieu-therapy, would be less likely to be immediately placed on antipsychotic medications after leaving the hospital than patients who were already being treated with antipsychotic medications at dis-

charge. During the late 1950s and early 1960s, when these data were gathered, there was already some evidence that maintenance treatment helped prevent relapse; however, the use of maintenance medication was not widely accepted. Today, maintenance therapy with antipsychotic medications is used during times of relative health to prevent future relapses, and is a widely accepted practice.

It might be expected that the greatest difference in rehospitalization days would have occurred in year one, when there was also the greatest difference in the amount of antipsychotic medication both groups of patients were receiving. The difference in the number of rehospitalization days, however, did not occur until the second year of follow-up. To determine whether having been treated more aggressively (in terms of chlorpromazine equivalents) during the first year after discharge had an effect lasting into the second year, a group matching technique (nearest mean adjustment analysis) was used to roughly equate the groups for year one. After the matching technique was run, the patients left in the initially medicated group still required fewer rehospitalization days in year two than the initially non-medicated group, suggesting that maintenance treatment during the first year was not the sole reason there was a greater number of rehospitalization days during the second year for the initially non-medicated group.

Using length of first hospital stay as the criterion for better prognosis patients

Choosing a period of time until discharge longer than 6 months after first admission would not have restricted the study to only 'better prognosis' patients. Choosing a period of less than 6 months would not have provided any useful information, since so few patients from the initially non-medicated group could have been included.

Since those patients in the initially non-medicated group included in this study were judged able to leave the hospital within 6 months, by definition they were better responders and would have been expected to do relatively well regardless of their treatment; as a group they did not. One reason these patients did worse than expected is that the truly good responders may have been excluded from the initial study. May and his colleagues went to great lengths to pick

patients who would be relatively homogeneous with regard to prognosis. Patients were excluded from the study if they were considered to have little chance of leaving the hospital in less than 2 years, or if they were already showing signs of rapid recovery during the pre-study evaluation period of 16 days. While excluding those patients who were recovering rapidly without medications in the evaluation period may have eliminated the best prognosis patients, it is unlikely that patients who had spontaneous recoveries during the evaluation period would fit current diagnostic criteria for schizophrenia. These criteria require one month of significant symptoms and 6 months of continuous signs of disturbance; the patients eliminated from the study because of rapid improvement during the evaluation period might today be diagnosed with, for example, schizophreniform disorder (APA, 1994).

Role of support outside the hospital

It could be argued that the patients initially treated with antipsychotic medications were better stabilized and had a better chance to reintegrate themselves into the community; they would thus encounter less demoralization, stigmatization, and fragmentation of their families. Since both groups were hospitalized for the same amount of time, it seems unlikely that the poorer outcome of the initially non-medicated patients can be attributed to less community support. Also, the fact that the initially non-medicated patients did not require more rehospitalization days until the second year after their initial discharge suggests that they, at least superficially, were able to re-integrate themselves into their communities and families as successfully as the patients initially treated with medications.

The number of rehospitalization days could be related to important ancillary factors, such as the inability to obtain suitable care, or the absence of appropriate housing. Unfortunately, detailed information about the psychological and social stabilization of these patients, although initially collected, is no longer available. Nevertheless, since patients were randomly assigned to the treatment groups, there is no reason to believe that patients assigned to the initially non-medicated group came from families less able to provide for them. Indeed,

the two groups who were discharged within 6 months appeared to be reasonably well matched on potential indicators of outcome (age at first admission, gender, educational level, and marital status).

Public health considerations

There is now considerable evidence (Crow *et al*. 1986; Wyatt, 1991, 1995*b*; Loebel *et al*. 1992; Waddington *et al*. 1995) that not treating schizophrenia early in its course may affect the long-term morbidity of the illness. Similar findings have been described for manic depressive illness (Post *et al*. 1992), as well as for a variety of other illnesses, such as epilepsy. These effects go beyond the obvious acute effects of demoralization and stigmatization associated with being psychotic, and they also go beyond the dangers of suicide and potential violence. Unfortunately, the study by May and colleagues was not designed to deal directly with this question, and all other studies have approached it retrospectively.

Today, whether or not it is due to concern about long-term morbidity, first admission patients with a presumptive diagnosis of schizophrenia are unlikely to be kept off antipsychotic medications for more than a few days. Keeping first admission patients off medications for limited periods of time is done to comply with the patient's wishes, or for diagnostic or research purposes. There is, however, no evidence that a few days or weeks of untreated schizophrenia increases long-term morbidity. The onset of the illness for patients in the present study was certainly many weeks, months, and perhaps even years prior to their being entered into the study. Furthermore, the initially non-medicated patients in the present study were probably not given antipsychotic medications until they seemed to require them, well after leaving the hospital. Thus, because of the long period of time in which the patients were kept medication free, the results of the present analysis probably have little relevance for current clinical practice. Studies are necessary, however, to determine how early in the course of the illness intervention can be helpful in preventing long-term morbidity (Falloon, 1992).

Finally, it is important to stress that the results of this analysis do not address the issue of

any short- or long-term morbidity which may occur from taking stabilized patients with schizophrenia off medications. Because antipsychotic medications are not innocuous, and because some patients do recover after a single episode, it is usual practice to attempt to taper and discontinue them in first admission patients with schizophrenia after the first or second year of maintenance treatment (Kissling, 1991). Currently, the only accepted method of determining which patients will need to remain on medications indefinitely is by careful and watchful trial and error. This serious issue is one that requires considerably more scientific attention (Wyatt, 1995a).

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