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Psychotic relapse and maintenance therapy in paranoid schizophrenia: a 15 year follow up

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Abstract In spite of numerous reports on a 1 to 2 year maintenance neuroleptic treatment of schizophrenia, there is little systematic information on decade-long maintenance therapy. We conducted a retrospective study in fifty outpatients with paranoid schizophrenia who have been seen at our clinic for a duration of 15 years or more since their first psychotic episodes. Relapse rate within 2, 5, 10, and 15 years from remission of the first psychotic episode were 52, 60, 86, and 90%, respectively. However, the incidence of relapse decreased with time. This decrease was accounted for by the decrease of relapse observed when off drug. Conversely, the incidence of relapse occurred on drug remained unchanged. The average maintenance dose 15 years after remission of the first psychotic episode was 5.41 ± 7.28 mg/d (haloperidol equivalents: mean ± SD). The maintenance dose correlated significantly with the number of relapses and total duration of psychotic episodes. These results suggest that maintenance treatment remained effective for decades, although it did not ameliorate the liability to relapse itself. Repeated relapse may be associated with requirement for a higher neuroleptic dose for relapse prevention.

Key words Schizophrenia · Neuroleptics · Maintenance therapy · Relapse · Long-term course

Introduction

Maintenance antipsychotic drug treatment has proven highly effective in preventing psychotic relapse in placebo-controlled studies in patients with schizophrenia (for review, see Kane and Lieberman 1987, Kissling 1992). These studies have shown that neuroleptic treatment decreases the risk of relapse over a 2 to 5 year observation period. It has also been shown that discontinuation of maintenance medication often results in psychotic relapse in patients who have been in good remission (for review, see Kissling 1992, Gilbert et al. 1995). In these studies, the duration of remission before neuroleptic withdrawal ranged from 0.5 to 5 years, and the duration of observation off-drug ranged from 1 month to 2 years. Based on available studies, Kissling (1992) recommended a minimum of 1 to 2 years of neuroleptic maintenance therapy for first-episode schizophrenia and 5 years for multi-episode patients.

Empirically, a substantial number of patients seem to need very long, sometimes life-long, maintenance therapy. However, probably due to methodological difficulties, there is little systematic information on very long-term maintenance therapy. The appropriate duration and the optimal dose of prophylactic neuroleptic treatment for these patients are, therefore, controversial (Johnson et al. 1983, Johnson 1984). Further, it is not known whether the initially effective prophylactic dose would be necessary or sufficient for relapse prevention over time, or whether decade-long continuous neuroleptic medication would ameliorate the liability to relapse itself.

In order to examine the role of long-term maintenance therapy, we conducted a retrospective chart review in fifty outpatients with paranoid schizophrenia who had been seen at our clinic for a duration of 15 years or more since their first psychotic episode. Patients' clinical status as well as their neuroleptic doses (expressed as haloperidol equivalents) at each visit during this time period were examined using clinical records. The incidence of relapse after the first episode with or without drug discontinuation was analyzed. Also examined were associated factors which might have effects on the incidence of relapse as well as on the maintenance dose of neuroleptic drugs. These factors include sex, age, age at illness onset, duration of illness, total duration of drug treatment, number of hospitalizations, number of psychotic relapses, and total duration of psychotic episodes.

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Subjects and methods

The clinical records of schizophrenic subjects who had their first psychiatric episode before 1981 and who were attending the department of psychiatry of Hokkaido University Hospital were scrutinized. Patients who were on maintenance therapy in the year of this investigation (1996) and who had a past history of hallucinations and delusions were eligible for the study. Those whose age of onset was after 40 were excluded. The clinical records were reviewed by the investigators to select patients whose past psychotic episodes meet the ICD-10 criteria for paranoid schizophrenia. A total of 59 patients were identified but 9 patients were actively psychotic in the full year of 1996. They were found to have active symptoms continuously for years (9 to 21 years), in spite of continuous neuroleptic medication. These nine patients were excluded from the present study because its aim was to investigate the role of maintenance neuroleptic therapy. The sample size for this review was, therefore, 50 subjects.

The clinician responsible for each patient's management made the decisions regarding the selection of medication and its dosing. The patient's physician in most cases changed several times, because residents and staff psychiatrists had moved in and out the University Hospital during the 15 or more years of this follow-up study. When patients needed hospitalization, they were admitted either at the University Hospital or at one of its affiliated facilities.

The patients' clinical status, their age at onset of illness, the number of relapses and hospitalizations, as well as their neuroleptic dosing history, and their medication status at the time of relapse were recorded from the charts since their first visit through 1996. Age at onset of illness was determined by means of first appearance of psychotic symptoms. Relapse was defined as a clinically significant deterioration resulting in either the need for hospitalization, temporary withdrawal from work, or a change (or reinstitution) of medication. The duration of each relapse episode was estimated by month.

The frequency of relapse by the 2nd, 5th, 10th, and 15th year after remission of the first episode as well as by the end of this review (1996) was calculated. The mean follow-up duration after remission of the first episode was 21.7 ± 4.6 (SD) yr. In a similar manner, the mean incidence of relapse, when patients were either on or off maintenance medication, was calculated for the three successive five year epochs from remission of their first episode. Correlations between the number of relapse and either the age, age at onset, duration of illness or duration of pharmacotherapy were calculated at 5, 10, 15 years after remission of the first episode and up to 1996.

The neuroleptic doses were expressed as haloperidol-equivalents (HPE), using mainly the equation of Suy et al. (1982) and supplementally that of Ito (1985). The average yearly maintenance dose at the 5th, 10th, and 15th year after remission of the first episode as well as that during 1996 was calculated. When relapse had occurred in those particular years, the average yearly HPE dose was calculated excluding medication during the relapse. Correlation between the HPE and either the age, age at onset, duration of illness, total duration of drug treatment, number of relapses, number of hospitalizations or duration of psychotic period was calculated at 5, 10, and 15 years after the first remission as well as at 1996.

Comparison of demographic characteristics between male and female subjects in the psychiatric history was analyzed by *t*-tests. Duration of first, second, third, fourth, and fifth relapses was also compared by *t*-tests. Comparison of the incidence of relapse in each five year epoch as well as HPE dose at the 5th, 10th, 15th year after the first remission and at study end in 1996 was carried out by paired *t*-tests. Correlations were expressed using Pearson's correlation coefficients.

Results

The demographic characteristics and psychiatric history of the subjects at the end of the follow-up period (i.e., 1996) are shown in Table 1. There were more male than female patients. There were no differences in their age, age at onset of illness, number of hospitalizations nor average maintenance neuroleptic dose in 1996 between male and female. However, female patients had a significantly greater number of relapses (mean ± SD, 5.06 ± 2.38 vs 3.65 ± 1.95, $t = 1.60$, $p = 0.03$) and a significantly longer total duration of psychotic episodes (the sum of durations of relapses in months) than male patients (mean ± SD, 29.38 ± 14.71 vs 17.65 ± 9.81, $t = 3.34$, $p = 0.0016$).

Table 2 and Fig. 1 illustrate the frequency of relapse among the sample within 2, 5, 10, and 15 years from remission of their first psychotic episode and through the end of the observation period in 1996. Only 5 patients (10%) remained relapse-free while 21 patients (42%) relapsed 4 times or more times throughout the entire follow-up period (21.7 ± 4.6 years). The total number of relapses at either 5, 10 or 15 years after the first remission as well as at study end (1996) was not correlated with either the age or age at onset of illness. However, the total number of relapses was significantly correlated with the duration of illness ($R = 0.412$, $p = 0.0024$) and duration of pharmacotherapy ($R = 0.378$, $p = 0.0056$) at study end in

Table 1 Demographic characteristics and psychiatric history of the subjects. No. of hospitalizations and relapses as well as total duration of psychotic episode reflect the whole observation period

Sex	
Male	34
Female	16
Marital status	
Married	22
Never married	24
Divorced	4
Education, yr (mean ± SD)	14.0 ± 2.0
Age, yr (mean ± SD)	47.6 ± 8.7
Age at onset of illness, yr (mean ± SD)	25.1 ± 7.0
No. of hospitalizations (mean ± SD)	1.56 ± 1.81
No. of relapses (mean ± SD)	4.0 ± 2.18
Total duration of psychotic episodes, month (mean ± SD)	21.4 ± 12.7
Mean maintenance dose in the year of 1996 (mg/day haloperidol equivalence)	6.44 ± 8.11

Table 2 Actual number (percentage in the parenthesis) of patients who remained relapse-free, relapsed once, twice, three times, or four times or more times at 2, 5, 10, and 15 year after remission of the first episode as well as at the end of observation period (1996)

Number of relapses	Time after first-episode (year)				In 1996
	2	5	10	15	
None	24 (48)	12 (24)	7 (14)	5 (10)	5 (10)
Once	23 (46)	18 (36)	14 (28)	11 (22)	9 (18)
Twice	3 (6)	14 (28)	9 (18)	8 (16)	6 (12)
Three times	0 (0)	4 (8)	11 (22)	13 (26)	9 (18)
Four times or more	0 (0)	2 (4)	9 (18)	13 (26)	21 (42)

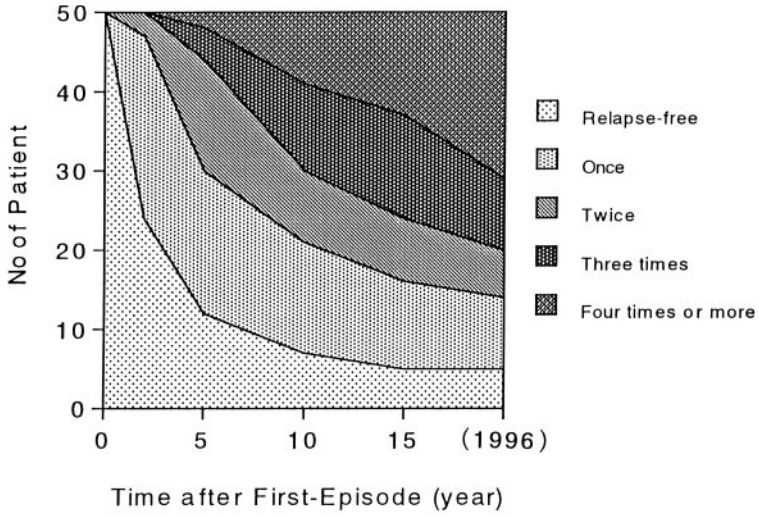

Fig. 1 Ratio of patients who remained relapse-free, relapsed once, twice, three times, or four times or more times. Abscissa indicates year after remission of the first episode. The year of 1996 corresponds 21.7 ± 4.6 (mean ± SD) year after remission of the first episode

Table 3 Incidence of relapse in the three successive 5 year epochs (1st–5th yr, 6th–10th yr and 11th–15th yr) after remission of the first episode expressed as relapses/patient/5 years (mean ± SD). "On drug" and "Off drug" indicate relapse occurred when on and off drug, respectively

	1st–5th year	6th–10th year	11th–15th year
Total no of relapses	1.32 ± 1.06	0.76 ± 0.77[a]	0.46 ± 0.73[a,b]
On drug	0.52 ± 0.74	0.38 ± 0.67	0.36 ± 0.63
Off drug	0.80 ± 0.99	0.38 ± 0.53[a]	0.10 ± 0.30[a,c]

[a] $p < 0.01$ compared with 1st–5th yr; [b] $p < 0.04$ compared with 6th–10th yr; [c] $p < 0.01$ compared with 6th–10th yr

1996, but not at either 5, 10 or 15 years after the first remission.

Sixty six percent of patients (33/50) had stopped their medication at least once during the follow up period. Of the total number of 207 relapses seen in the 50 patients in the observation period reviewed, 74 relapses (35.7%) occurred when patients were off medication. Approximately one thirds of relapses (25/74) occurred in patients off medication for more than 12 months while two thirds (49/74) occurred in those patients off medication less than 12 months. Table 3 summarizes the incidence of relapse in the three successive 5 year epochs. The total incidence of relapse (number of relapses/patient/5 years) was found to decrease significantly from the first to the second 5 year-period ($t = 3.51$, $p = 0.001$), and from the second to the third 5 year-period ($t = 2.13$, $p = 0.04$). There were also significant reductions in the incidence of relapses that occurred off medication from the first to the second 5 year-period ($t = 3.13$, $p = 0.003$) and from the second to the third 5 year-period ($t = 3.26$, $p = 0.002$). However, the incidence of relapse on medication did not change significantly throughout the three 5 year-periods.

After the first remission, the duration of subsequent psychotic relapses did not change over time. The average episode duration in months (mean ± SD) was 9.90 ± 9.36 ($n = 50$), 3.31 ± 2.46 ($n = 45$), 3.44 ± 2.41 ($n = 36$), 4.6 ± 6.36 ($n = 30$), and 3.57 ± 3.04 ($n = 21$) in the first through fifth episode, respectively. The first episode was significantly longer than others ($t = 4.57$, $p = 0.0001$ vs second, $t = 4.04$, $p = 0.0001$ vs third, $t = 2.74$, $p = 0.0076$ vs forth, $t = 3.02$, $p = 0.0035$ vs fifth), apparently because it includes a longer untreated period.

Mean (± SD) of HPE (mg/d) was 3.20 ± 3.18, 4.75 ± 5.44, 5.41 ± 7.28, and 6.44 ± 8.13 in the 5th, 10th, 15th year after the first remission and at study end, respectively. There was a significant increase in HPE dose from the 5th to the final year of observation (1996) ($t = 2.695$, $p = 0.0096$). There was also a nonsignificant trend toward an increase in HPE dose from the 5th to 10th ($t = 1.84$, $p = 0.07$), and from the 5th to 15th year ($t = 1.97$, $p = 0.055$). However, as shown in Fig. 2, there was a substantial number of patients in whom the dose had remained low continuously for 15 years or more, while there are some in whom the dose had gradually increased. In the final year of observation (1996), HPE dose was ≤ 1 mg/d in 14 patients, ≤ 3 mg/d in 28 patients, and ≥ 8 mg/d in 13 patients.

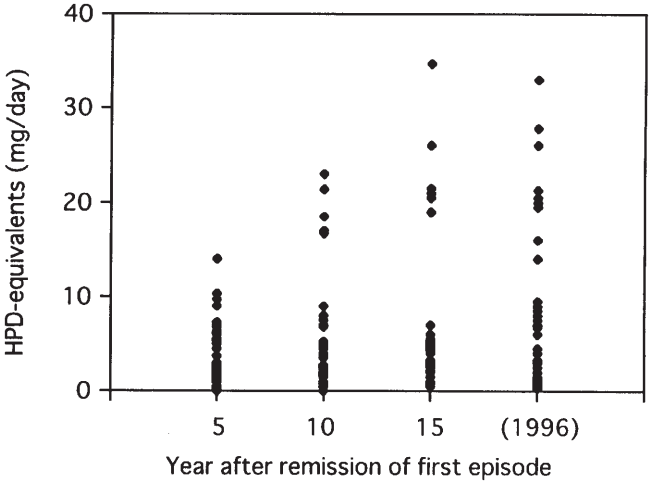

Fig. 2 Maintenance dose of neuroleptics in 50 patients at 5, 10, and 15 years after remission of the first episode as well as at the end of observation period in 1996

Table 4 Correlations of background variables with maintenance dose in fifty paranoid schizophrenic patients. For the age, age at onset of illness, duration of illness and duration of medication, values at the end of observation period in 1996 are shown

Background variables	Correlation	
	Pearson's *r*	*p*
No. relapses		
at 1996	0.48	0.0003
at 15th yr	0.31	0.03
at 10th yr	0.25	0.08
at 5th yr	0.13	0.38
No. hospitalizations		
at 1996	0.5	0.0002
at 15th yr	0.17	0.24
at 10th yr	0.21	0.14
at 5th yr	0.037	0.8
Total duration of psychotic episodes		
at 1996	0.34	0.015
at 15th yr	0.44	0.002
at 10th yr	0.19	0.18
at 5th yr	0.31	0.03
Age	0.023	0.87
Age at onset of illness	0.007	0.96
Duration of illness	0.056	0.7
Duration of medication	0.035	0.81

As shown in Table 4, there were significant correlations between the maintenance HPE dose and the number of psychotic relapses, the number of hospitalizations, and the total duration of psychotic episodes at the end of the observation period. The correlation between the maintenance dose and the number of relapses was also significant at 15 years after remission of the first episode. Correlation between the maintenance dose and the total duration of psychotic episodes was also significant at the 5th and 15th year after remission of the first episodes. No significant correlations were found between the HPE dose and either the age, age at onset of illness, duration of illness or the total duration of medication at either 5, 10 or 15 years after remission of the first episode or by 1996.

Discussion

The present study analyzed psychotic relapse of paranoid schizophrenic patients who received long-term (more than 15 years) maintenance treatment in an outpatient clinic. It was noted that many of the patients relapsed during the clinical course. The relapse rate within 2 years after remission of the first psychotic episode was 52% (26/50). In 69% (18/26) of relapsed patients, the relapse was associated with drug discontinuation. Although the present study is a retrospective survey of daily clinical practice, this rate falls within a range compatible with the result of previous controlled studies. Relapse rates in first break schizophrenics have been reported 0% on neuroleptic medication and 41% on placebo within one year (Kane et al. 1982), or 58% on medication and 70% on placebo within two years (Crow et al. 1986). This study showed that relapse rate progressively increased with time. By the 5th year after the first episode, 60% of patients relapsed while 40% already relapsed two or more times. Relapse rates continued to rise to 86% by the 10th year and to 90% after the 15th and remaining year of observation (21.7 ± 4.6 years after remission of the first episode; mean ± SD). Two or more relapses occurred in 58%, 68%, and 72% of patients by the 10th, 15th, and last year of observation (1996), respectively.

The incidence of relapse, however, was found to decrease with time. The number of relapses in the first three five year epochs after remission of the first episode was 1.32 ± 1.06, 0.76 ± 0.77, and 0.46 ± 0.73, respectively (number of relapses/patient/5 years, mean ± SD). This decrease was accounted for by the decrease of relapse observed when off drug. The number of relapses which occurred off drug was 0.8 ± 0.99, 0.38 ± 0.53, and 0.1 ± 0.30 in the first three five year epochs, respectively (number of relapses/patient/5 years, mean ± SD). It is suggested that better compliance was gradually achieved and contributed to the lower incidence of relapse in the later years. Conversely, the incidence of relapse that occurred on maintenance medication was not different among the three 5-year periods. These results suggest that the efficacy of maintenance therapy remained unchanged during the 15 or more years these patients were followed. The results also suggest that the liability to relapse itself did not ameliorate even after decades-long prophylactic neuroleptic treatment. This suggestion is consistent with a notion, although based on data from a shorter period of observation, that drug treatment does not cure the underlying morbidity of schizophrenia (Johnson et al. 1983, Curson et al. 1985).

The average maintenance dose gradually and significantly increased during the 15 or more years of treatment. However, it was noted that many patients remained on low dose neuroleptics. In 28% (14/50) of the patients, the maintenance dose after a mean follow up of 21.7 ± 4.6 (mean ± SD) years from first remission was ≤ 1 mg/d HPE. In 56% (28/50), the dose was ≤ 3 mg/d HPE. Previous studies have reported that low dose neuroleptics are sufficient for relapse prevention in a large proportion of patients (Kane 1983, Marder 1987, Johnson 1987, Hogarty 1988). Follow-up periods in those studies, however, ranged from 1 to 2 years. This present study corroborated this finding since in a substantial proportion of patients, a low dose maintenance therapy was still an effective treatment even 15 or more years after onset of illness.

It is also known, however, that underdosing of maintenance neuroleptics can lead to relapse. The risk of relapse has been shown to be greater in patients with a low dose rather than a standard dose of long-acting injectable neuroleptics (Kane et al. 1983, Marder et al. 1987, Johnson et al. 1987, Hogarty 1988, Kane et al. 1993, Schooler et al. 1997). Reduction of neuroleptic dose also can increase the risk of relapse (Johnson 1987). These studies suggest that

the maintenance dose has an influence on the risk of relapse, although the minimal effective dose of neuroleptics to prevent relapses varies among patients (Baldessarini and Davis 1980, Johnson 1984). In the present study, there was a significant increase in the maintenance dose over the years. To investigate which factors were associated with the maintenance neuroleptic dose, various background variables were correlated with HPE dose. HPE dose showed no correlation with either the age, age at illness onset, duration of illness or total duration of drug treatment. Thus, it seems unlikely that these variables have effects on the maintenance dose.

Interestingly, HPE dose correlated significantly with the number of psychotic relapses, number of hospitalizations, and the total duration of psychotic episodes at the year of this investigation. There was also a significant correlation between the neuroleptic dose and the total duration of psychotic episodes at the 5th and 15th year after remission of the first episode. A significant correlation was also noted between the neuroleptic dose and the number of relapses at 15 years after remission of the first episode. These results suggest that those patients with the greatest number of relapses and the longest total duration of psychotic episodes took the highest prophylactic neuroleptic dose. Johnson et al. (1983) have suggested that relapse may be related with an increase of the maintenance dose. They found that most patients who discontinued dopot maintenance therapy relapsed, and hence resumed neuroleptic therapy, but afterward needed higher maintenance doses than those continuously on medication. Our results may support their observation.

An alternate interpretation of these findings may be that repetitive psychotic relapse leads to a lower threshold for relapse and consequently requires a higher neuroleptic dose for prevention. This interpretation is not fully supported by solid evidence but several studies partially support this notion. Several studies found that a longer duration of active illness was associated with poorer outcome or poorer neuroleptic response (Coryell and Tsuang 1982, Rabiner et al. 1986, McEvoy 1991). This finding was recently confirmed by Loebel et al. (1992) who conducted a study with first-episode schizophrenic patients using standardized treatment and uniform assessments. They found that a longer duration of illness before the beginning of neuroleptic treatment was associated with a longer time to remission as well as with a lower level of remission. In agreement with their finding, Szymanski et al. (1996) found an association between duration of illness before treatment and poor outcome in both first-episode and chronic schizophrenia.

The duration of active psychotic symptoms also may have an influence on long-term outcome and relapse. May et al. (1981) reported that patients treated with neuroleptic drugs or electroconvulsive therapy (ECT) in their first episode had a much better outcome in the subsequent three years than a group treated initially without drugs or ECT, who spent a longer time in hospital for their first episode. Reanalyzing their data, Wyatt (1991) showed that this difference in outcome was not accounted for by the difference in the neuroleptic medication during the three-year follow up period. Lo and Lo (1977) found that a shorter duration of untreated illness prior to the initial acute episode was significantly associated with favorable outcome after 10 years. More specifically, Crow et al. (1986) found an association between duration of active psychosis and later incidence of relapse. In a two-year, placebo-controlled trial of maintenance medication with first-episode schizophrenic patients, they found that the most important determinant of relapse in either patients who took active medication or placebo for maintenance was duration of illness prior to receiving treatment for their first episode. These studies suggest an association among persistence of active pathophysiology, poor neuroleptic response, and frequent relapse. It is possible, therefore, that repeated relapse results in lasting morbidity that might necessitate a higher maintenance dose for future relapse prevention. As has been pointed out (Baldessarini and Davis 1980, Johnson 1984), the optimal maintenance dose varies among patients. In the light of the present study, the number of previous relapses may be a key factor associated with defining appropriate maintenance neuroleptic dosing.

There are several limitations in the present study that are intrinsically associated with any retrospective case record survey. One such limitation may be sample bias. Patients who did not relapse without maintenance medication were naturally precluded from this study. It should also be noted that patients who needed long-term hospitalization may have been transfered from our clinic to affiliated hospitals. Furthermore, patients who had continuous paranoid symptoms were excluded from this study. Obviously, the subjects of this study are not a representative sample of paranoid schizophrenic patients in general. Male subjects dominated in this study, which is a common finding in schizophrenia research (Iacono 1992, Lindstroem 1994). However, the finding in this study that women had more relapses is not consistent with previous reports that showed they had fewer relapses (Watt 1983) and fewer rehospitalizations (Salokongas 1983, Goldstein 1988). These latter studies included not only the paranoid type but also other types of schizophrenia while the follow-up periods were only 5 to 9 years. These discrepancies could be related to differences in the study design. Alternatively, it is possible that female patients with the best prognosis could have been excluded from the present study.

Another important limitation of this study may be that the neuroleptic dosing in each subject was not systematically adjusted, but rather it was administered empirically in standard clinical practice. When patients showed stable remission continuously, the dose was cautiously reduced. When they relapsed or showed prodromal signs of psychotic symptoms even on medication, the maintenance dose was slightly increased. Voluntary drug discontinuation was often noted during the long clinical course. However, as was indicated by the decrease in the incidence of drug discontinuation in the later years, compliance among the subject of this study seemed to improve during the

15 or more years of their clinical management. Taken together, it can be assumed that the prescribed maintenance dose at the time of the investigation had become close to the minimal effective dose.

In spite of numerous reports on a 1 to 2 year maintenance treatment of acute schizophrenia, there is little systematic information on decade-long maintenance therapy. It would be extremely difficult to conduct such a long-term controlled study, due to methodological, ethical, and practical reasons. In spite of the limitation of the present retrospective study, its results provided empirically based data on long-term maintenance pharmacotherapy in chronic schizophrenia. Further studies, however, are necessary to generalize these present findings.

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