Comparison of Time to Rehospitalization Among Schizophrenic Patients Discharged on Typical Antipsychotics, Clozapine or Risperidone

Ching-Hua Lin, Shih-Chi Lin, Ming-Chao Chen, Shing-Yaw Wang*
Kai-Suan Psychiatric Hospital, Kaohsiung, Taiwan, R.O.C.

Background: The purpose of this study was to compare the time to rehospitalization of schizophrenic patients who were discharged from a psychiatric hospital while being treated with typical antipsychotics, clozapine or risperidone. We also assessed other possible predictors of time to rehospitalization.

Methods: The study monitored the rehospitalization status of all the schizophrenic patients who were discharged from a psychiatric hospital between July 1, 2001 and June 30, 2002 while they were taking typical antipsychotics (n = 272), clozapine (n = 61) or risperidone (n = 49). Rehospitalizations were tracked over a 2-year period using the Kaplan-Meier method. Risk factors associated with rehospitalization were examined by the Cox proportional hazards regression model.

Results: No significant differences in time to rehospitalization were observed among the groups in the first or second year after discharge. Age at onset of schizophrenia was a risk factor for time to rehospitalization over the 1- and 2-year periods.

Conclusion: This study demonstrated that atypical antipsychotics did not lengthen the time to rehospitalization. The earlier the age at onset of schizophrenia, the shorter is the time to rehospitalization. Some other factors thought to impact rehospitalization need to be further assayed. [*J Chin Med Assoc* 2006;69(6):264–269]

Key Words: age at onset, clozapine, rehospitalization, risperidone, schizophrenia

Introduction

Schizophrenia is a chronic disorder. Without treatment, the symptoms generally wax and wane. The major goal of long-term treatment in schizophrenic patients is to sustain symptom remission and prevent relapse. Relapse in schizophrenia is a relative term reflecting symptomatic worsening, violence, or suicidal behavior. Relapse often leads to rehospitalization.

Typical antipsychotic medications have been shown to reduce rehospitalization rates in patients with schizophrenia. By survival curve analysis, Weiden and Olfson[1] estimated that 49.2% of all stabilized schizophrenic patients treated with typical antipsychotics would be rehospitalized within 1 year, and 80.9% of patients within 2 years. The high rehospitalization rate is associated with poor long-term prognosis and outcome.[2] Nonadherence to medication is the most important factor leading to relapse and rehospitalization in schizophrenia.[3,4] Weiden and Olfson[1] suggested that rates of medication nonadherence among outpatients with schizophrenia have been found to approach 50% during the first year after hospital discharge, and the risk of relapse has been found to increase by at least 100% in patients who skip their drug treatment. Factors related to nonadherence have also been identified as predictors of relapse and rehospitalization.[5]

*Correspondence to: Dr. Shing-Yaw Wang, Kai-Suan Psychiatric Hospital, 130, Kai-Suan 2nd Road, Ling-Ya District, Kaohsiung 802, Taiwan, R.O.C.
E-mail: chua.lin@msa.hinet.net • Received: July 25, 2005 • Accepted: April 11, 2006

Depot antipsychotics were developed to assist patients to adhere to long-term drug therapy.[6] The rehospitalization rate may be decreased with the combination of depot antipsychotics and psychosocial interventions.[7,8] Although oral or depot typical antipsychotics can prevent rehospitalization in patients with schizophrenia, higher rates of extrapyramidal side effects for these types of antipsychotic medication may be associated with higher rates of nonadherence. Thus, patients prescribed these types of antipsychotics may, as a secondary effect, have higher rates of rehospitalization.

Atypical antipsychotics such as clozapine, risperidone, olanzapine and quetiapine are associated with lessened side effects when compared to the typical agents.[9] Presumably, adherence to atypical antipsychotics should be better, and, therefore, relapse and time to rehospitalization longer or rehospitalization rate lower. But the results of some studies comparing the rehospitalization rates of schizophrenic patients taking typical or atypical antipsychotics have been controversial.

The first study to compare the rehospitalization rates of schizophrenic patients discharged while taking risperidone or clozapine was reported by Conley et al.[10] They found that, at 24 months, 13% of the clozapine-treated patients and 34% of the risperidone-treated patients were readmitted. There were no significant differences in rehospitalization rates between the patients receiving risperidone and those receiving clozapine. But the lack of a typical antipsychotic comparison group and the small samples (49 *vs.* 75 subjects) were the limitations of that study.

A study from Israel, conducted by Rabinowitz et al,[11] found the rehospitalization rate with risperidone (33%) or olanzapine (31%) to be significantly lower than the rate with typical antipsychotics (48%) for 24 months following discharge, but not for 12 months. The study demonstrated that atypical antipsychotics could reduce the use of hospital services in patients with schizophrenia for a 2-year follow-up period.

Patel et al[12] compared rehospitalization rates over a 1-year period among patients discharged while receiving risperidone, olanzapine or typical antipsychotics, and found that at 12 months, 34% of the olanzapine-treated patients, 35% of the risperidone-treated patients, and 20% of the typical antipsychotics-treated patients were readmitted. Typical antipsychotics were associated with lower rehospitalization rates in a 1-year period relative to the 1-year rates for atypical antipsychotics. However, these differences were not significant. It is likely that the 1-year follow-up period was not enough to observe the significant differences. But in the 3 above-mentioned studies, the authors never illustrated the continuous time data on whether or not patients had been lost to follow-up or had been switched to another class of antipsychotic during outpatient follow-up.

In a randomized, double-blind, prospective study to compare the prevention of relapse in schizophrenia with risperidone or haloperidol over about a 2-year period, there was no significant difference in the rehospitalization rates between the 2 groups.[13]

In this study, we compared the time to rehospitalization of schizophrenic patients taking typical antipsychotics, clozapine or risperidone under naturalistic conditions. We also evaluated the factors related to the risk of rehospitalization over a 2-year period.

Methods

The study's subjects consisted of all the schizophrenic patients who were discharged between 1 July 2001 and 30 June 2002 from Kai-Suan Psychiatric Hospital (a public mental hospital with 800 beds) while taking typical antipsychotics, clozapine or risperidone. Clozapine and risperidone were the only atypical antipsychotics used in this hospital. In order to control pharmacy costs before September 2001, Taiwan, R.O.C.'s Bureau of National Health Insurance instructed that atypical antipsychotics be limited to treatment-resistant schizophrenic patients, psychotic patients who experienced severe side effects while taking typical antipsychotics, patients with organic mental disorders, and elderly patients.

Subjects' rehospitalization status was examined over a 2-year follow-up period, up to 1 July 2004. Successful discharge was defined as: (1) a patient who began with typical antipsychotics, clozapine, or risperidone treatment and was discharged on the same drug within 1 admission;[10] and (2) a patient discharged because symptoms improved. After discharge, all patients were followed up in the outpatient department of the same hospital. No special psychosocial interventions or community services (e.g., home visit, halfway house, community rehabilitation center, or day hospital) were provided for any of the patient groups.

Rehospitalization was defined as admission to Kai-Suan Psychiatry Hospital for a psychiatric reason. All patients were tracked for up to 2 years regarding readmissions. With the permission of the hospital's review board, chart reviews were performed by 2 senior psychiatrists (first and second authors) to verify the data. This study was approved by the human subjects committee of Kai-Suan Psychiatric Hospital to be exempt from the requirement for written informed consent.

Statistical analysis

Time to rehospitalization was estimated by the Kaplan-Meier method. The significance of differences among the 3 groups, divided based on which medication they were taking, was measured by the log-rank test. The univariate Cox proportional hazards regression model was used to analyze demographic data and the factors thought to affect clinical outcomes[14] as well as time to rehospitalization, including sex, marital status, family history of schizophrenia, comorbid alcohol abuse,[3] age, age at onset,[15] years of education, and days in hospital.[16] If multiple significant variables were identified, the forward Cox proportional hazards regression model was used to further analyze predictive factors related to rehospitalization. Age at onset was regarded as age at the first psychotic symptoms. Each subject's family history was taken, which included first-degree, second-degree, or third-degree blood relatives who had schizophrenia. The Pearson chi-square test was used to compare categorical variables. The Kruskal-Wallis test was used to compare continuous variables. All tests were two-tailed, and significance was defined as an alpha of less than 0.05. Data were analyzed with SPSS version 10.0 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

A total of 382 schizophrenic patients taking typical antipsychotics (n = 272, dosage = 568.1 ± 345.3 mg/day), clozapine (n = 61, dosage = 269.7 ± 153.6 mg/day) or risperidone (n = 49, dosage = 3.7 ± 1.6 mg/day) were recruited for the study. Characteristics of the 3 groups can be found in Table 1. No statistical differences among the groups were demonstrated with regard to sex, family history, comorbid alcohol abuse, age, or years of education. In the group treated with clozapine, patients had an earlier age at onset of psychosis and spent longer days in hospital.

Of a total of 272 patients taking typical antipsychotics, 213 (78.3%) were taking oral agents and 59 (21.7%) were receiving depot preparations. No significant differences existed in time to rehospitalization between the patients taking typical oral or depot antipsychotics at 360 days (log rank = 0.35, df = 1, p = 0.56) or at 720 days (log rank = 0.90, df = 1, p = 0.34).

Eighty-three patients (59 patients taking typical antipsychotics; 13 clozapine; 11 risperidone) were withdrawn during the 2-year period. The 3 groups were not significantly different in time to follow-up at either

Table 1. Characteristics of schizophrenic patients discharged while taking typical antipsychotics, clozapine or risperidone

Variable	Typical antipsychotics (n = 272)		Clozapine (n = 61)		Risperidone (n = 49)		Analysis		
	n	%	n	%	n	%	χ^{2*}	df	p
Sex							4.35	2	0.11
Male	149	54.8	40	34.4	33	67.3			
Female	123	45.2	21	65.6	16	32.7			
Married							4.96	2	0.08
Yes	61	22.4	8	13.1	15	30.0			
No	211	77.6	53	86.9	34	69.4			
Family history							4.38	2	0.11
Yes	47	17.3	17	27.9	7	14.3			
No	225	82.7	44	72.1	42	85.7			
Comorbid alcohol abuse							0.07	2	0.97
Yes	30	11.0	7	11.5	6	12.2			
No	242	89.0	54	88.5	43	87.8			
Depot antipsychotic use									
Yes	59	21.7	–	–	–	–			
No	213	78.3	–	–	–	–			
	Mean	SD	Mean	SD	Mean	SD	$\chi^{2\dagger}$	df	p
Age (yr)	39.2	10.0	37.2	8.0	41.5	14.5	2.47	2	0.29
Age at onset (yr)	25.4	8.6	22.3	6.2	27.0	10.5	7.88	2	0.02
Years of education	10.6	2.9	10.3	2.7	10.6	3.7	0.90	2	0.64
Days in hospital	136.7	293.4	229.9	281.2	95.2	77.7	24.24	2	0.00
Dose (mg/d)[‡] at discharge	568.1	345.3	269.7	153.6	3.7	1.6			

**Pearson chi-square test; †Kruskal-Wallis test; ‡chlorpromazine daily equivalent dose for typical antipsychotics.*

1 year (log rank = 3.12, df = 2, $p = 0.21$) or 2 years (log rank = 0.09, df = 2, $p = 0.95$) in the study. Figure 1 presents the time to rehospitalization for each of the 3 groups. Time to rehospitalization showed no significant differences within 360 days (typical antipsychotics, mean ± SD = 244 ± 8 days; clozapine, 220 ± 19 days; risperidone, 262 ± 19 days; log rank = 1.00, df = 2, $p = 0.61$) and 720 days (typical antipsychotics, mean ± SD = 378 ± 18 days; clozapine, 403 ± 42 days; risperidone, 426 ± 43 days; log rank = 1.14, df = 2, $p = 0.57$) after discharge, although the observed time to rehospitalization for the group receiving typical antipsychotics was shorter in the 2-year period. Table 2 displays the survival time, mean follow-up time, and event rate analyzed by the Kaplan-Meier method.

Using the univariate Cox proportional hazards regression model, out of sex, marital status, family history of schizophrenia, comorbid alcohol abuse, age at onset, age, years of education, and days in hospital, factors of borderline significance or of significance were marriage ($p = 0.053$) as well as age at onset ($p = 0.015$) at 1 year, and age ($p = 0.046$) as well as age at onset ($p = 0.020$) at 2 years. After further analysis by the forward Cox proportional hazards regression model, age at onset was found to be a predictor affecting time to rehospitalization within the 360-day (hazards ratio = 0.977, 95% CI = 0.958–0.995) and 720-day (hazards radio = 0.980, 95% CI = 0.963–0.997) periods (Table 3).

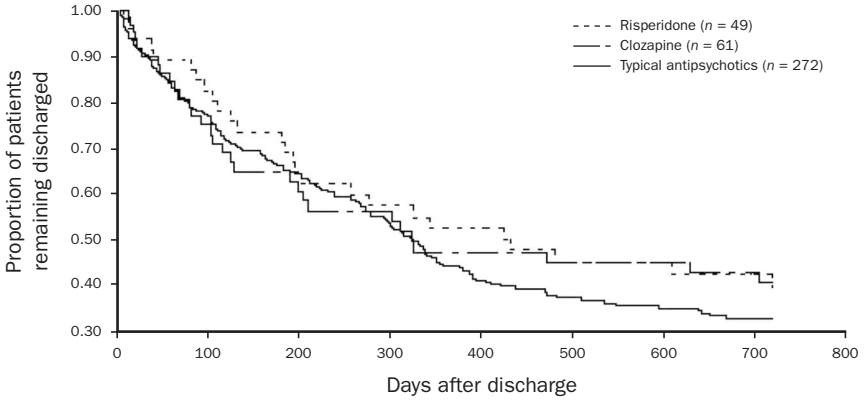

Figure 1. Time to rehospitalization for patients discharged while taking typical antipsychotics, risperidone or clozapine (log rank = 1.00, df = 2, $p = 0.61$ for 1-year period; log rank = 1.14, df = 2, $p = 0.57$ for 2-year period).

Table 2. Survival time, mean follow-up time, and event rate from Kaplan-Meier method

	Typical antipsychotics (n = 272)	Clozapine (n = 61)	Risperidone (n = 49)	p (log rank)
360-day follow-up period				
Mean survival time ± SD [95% CI] (d)	244 ± 8 [228–261]	240 ± 19 [204–276]	262 ± 19 [225–300]	0.61
Median survival time ± SD [95% CI] (d)	323 ± 24 [276–370]	323*	†	
Mean follow-up time ± SD [95% CI] (d)	315 ± 7 [302–328]	290 ± 17 [256–325]	331 ± 16 [300–362]	0.21
Event rate (%)	49.6	44.3	43.0	
720-day follow-up period				
Mean survival time ± SD [95% CI] (d)	378 ± 18 [343–413]	403 ± 42 [321–484]	426 ± 43 [341–510]	0.57
Median survival time ± SD [95% CI] (d)	324 ± 20 [285–363]	323 ± 223 [0.0–761]	431 ± 172 [94–768]	
Mean follow-up time ± SD [95% CI] (d)	561 ± 18 [526–596]	552 ± 41 [472–631]	601 ± 36 [531–671]	0.95
Event rate (%)	57.7	49.2	53.1	

**Standard deviation and 95% CI could not be calculated; †median survival time could not be calculated.*

Table 3. Factor affecting time to rehospitalization by the forward Cox proportional hazards regression model

Follow-up period (d)	Risk factor	B	Hazard ratio	95% CI	p
360	Age at onset	–0.024	0.977	0.958–0.995	0.015
720	Age at onset	–0.020	0.980	0.963–0.997	0.020

Discussion

No significant difference in time to rehospitalization was exhibited among patients on typical oral or depot antipsychotics at either 1 or 2 years. Atypical antipsychotics, clozapine or risperidone, did not increase time to rehospitalization during the 1- and 2-year follow-up periods. The group receiving clozapine had an earlier age at onset of psychosis and a longer length of hospital stay. This result may mean that most of the patients taking clozapine were treatment-resistant schizophrenics.

Age at onset contributed to the risk of time to rehospitalization in this study. Age at onset of illness can be defined as age at the first psychotic symptoms, age at first hospitalization, or age at first psychiatric consultation.[17] Corrigan et al[18] stated that patients with late-onset schizophrenia are rarely admitted to a state hospital. De Lisi[19] concluded that age at onset may determine the degree to which the brain undergoes structural change as well as cognitive impairments, and it may be a crucial determinant of outcome. Early age of onset is shown to be associated with longer duration of illness, more frequent extrapyramidal adverse effects of antipsychotics,[20] and poorer response to antipsychotics.[21] Poorer response to antipsychotics represents the more severe psychopathology following treatment and is easier to relapse.[5] The results of the current study suggest that the earlier the onset of schizophrenia, the shorter is the time to rehospitalization. This finding is consistent with the results of Eaton et al.[22] Compared to the other 2 groups, the group receiving clozapine had an earlier age at onset of psychosis, but did not have the significantly shorter time to rehospitalization. A possible explanation is that clozapine improves clinical outcome and increases time to rehospitalization in schizophrenic patients.

We could not demonstrate the significantly shorter time to rehospitalization in the group treated with typical antipsychotics. Neurologic side effects are dose-dependent. The study by Leucht et al[23] revealed that mean doses of chlorpromazine (CPZ) < 600 mg/day or its equivalent had no higher risk of extrapyramidal side effects than new-generation drugs. Most of the patients in this group received a medium dose of medication (568.1 ± 345.3 mg CPZ equivalents). The patients receiving typical antipsychotics may have been tolerant of the side effects of the medication.

In this study, we also could not prove the presumption that adherence to atypical antipsychotics should be better, and, therefore, relapse as well as time to rehospitalization longer. Poor adherence or nonadherence to treatment is considered to be one of the most important factors affecting outcome. Some studies were unable to obtain evidence that progress had been made in increasing adherence or insight, despite the advent of newer antipsychotic medications with less severe and disabling side effects.[24–26] If a patient stops taking medication during the stable phase, s/he may feel better, with less sedation or other side effects. As a result, the patient may come to the false conclusion that the medication is not necessary or does not have benefits.[27] Though we did not directly address some factors affecting time to rehospitalization, such as side effects and nonadherence to medication, in this study, treatment modalities only dependent on atypical antipsychotic use were not likely to be effective in lengthening the time to rehospitalization in schizophrenia. As in the study by Patel et al,[12] a limitation of our study was that all subjects were from the same hospital. But the advantage is that the review of patient charts gave us continuous time data. Another limitation was the small sample sizes of clozapine- and risperidone-treated groups in this study. Attrition of the study population due to losses through follow-up might have been minimized if the register had included all facilities in a sufficiently large catchment area. The other limitation of this study, similar to that in the studies of Conley et al[10] and Rabinowitz et al,[11] was that the patients were not randomly assigned to the drug treatments.

Future studies of the time to rehospitalization must be conducted in many different mental health systems in Taiwan to generalize the specific effects of antipsychotics on outcomes. Some variables thought to impact the time to rehospitalization, such as severity of psychopathology, insight into illness, level of family support, community services, or some other psychosocial factors related to medication adherence, also need to be researched.

Acknowledgments

This study was supported by a grant from Kai-Suan Psychiatry Hospital in 2004.

References

1. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophr Bull* 1995;21:419–29.
2. Sheitman BB, Lee H, Strauss R, Lieberman JA. The evaluation and treatment of first-episode psychosis. *Schizophr Bull* 1997; 23:653–61.
3. Sullivan G, Wells KB, Morgenstern H, Leake B. Identifying modifiable risk factors for rehospitalization: a case-control

study of seriously mentally ill persons in Mississippi. *Am J Psychiatry* 1995;152:1749–56.
4. Kent S, Yellowlees P. Psychiatric and social reasons for frequent rehospitalization. *Hosp Community Psychiatry* 1994;45:347–50.
5. Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS Drugs* 2002;16:473–84.
6. Janicak PG. *Handbook of Psychopharmacology*. Philadelphia: Lippincott Williams & Wilkins, 1999.
7. Hogarty GE. Prevention of relapse in chronic schizophrenic patients. *J Clin Psychiatry* 1993;54:18–23.
8. Schooler NR, Keith SJ, Severe JB, Matthews SM, Bellack AS, Glick ID, Hargreaves WA, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia. *Arch Gen Psychiatry* 1997;54:453–63.
9. Miller CH, Mohr F, Umbricht D, Woerner M, Fleischnacker WW, Lieberman JA. The prevalence of acute extrapyramidal signs and symptoms in patients treated with clozapine, risperidone, and conventional antipsychotics. *J Clin Psychiatry* 1998;58:69–75.
10. Conley RR, Love RC, Kelly DL, Bartko JJ. Rehospitalization rates of patients recently discharged on a regimen of risperidone or clozapine. *Am J Psychiatry* 1999;156:863–8.
11. Rabinowitz J, Lichtenberg P, Kaplan Z, Mark M, Nahon D, Davidson M. Rehospitalization rates of chronically ill schizophrenic patients discharged on a regimen of risperidone, olanzapine, or conventional antipsychotics. *Am J Psychiatry* 2001;158:266–9.
12. Patel NC, Dorson PG, Edward N, Mendelson S, Crismon ML. One-year rehospitalization rates of patients discharged on atypical versus conventional antipsychotics. *Psychiatr Serv* 2002; 53:891–3.
13. Csernansky JG, Mahmound R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002;346:16–22.
14. Kaplan HI, Sadock BJ, Grebb JA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences and Clinical Psychiatry*, 9th edition. Baltimore: Williams & Wilkins, 2003.
15. Haro JM, Eaton WW, Bilker WB, Mortensen PR. Predictability of rehospitalization for schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 1994;244:241–6.
16. Appleby L, Desai PN, Luchins DJ, Gibbons RD, Hedeker DR. Length of stay and recidivism in schizophrenia: a study of public psychiatric hospital patients. *Am J Psychiatry* 1993;150: 72–6.
17. Drnovsek MZ, Tavcar R. Age at onset of schizophrenia and neuroleptic dosage. *Soc Psychiatry Psychiatr Epidemiol* 1999; 34:622–6.
18. Corrigan PW, Gleason W, Cohler BJ, Luchins D, Addis I. Are there patients with late-onset schizophrenia in state hospitals? *Schizophr Res* 1995;15:261–4.
19. De Lisi LE. The significance of age at onset for schizophrenia. *Schizophr Bull* 1992;18:209–15.
20. Sandyk R, Kay SR. Drug-induced parkinsonism: relationship to age at onset of schizophrenia. *Funct Neurol* 1991;6:151–7.
21. Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, Thompson PA. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry* 1997;154:475–82.
22. Eaton WW, Mortensen PB, Herrman H, Freeman H, Bilker W, Burgess P, Wooff K. Long-term course of hospitalization for schizophrenia. I. Risk for rehospitalization. *Schizophr Bull* 1992;18:217–28.
23. Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003;361: 1581–9.
24. Young JL, Spitz RT, Hillbrand M, Daneri G. Medication adherence failure in schizophrenia: a forensic review of rates, reasons, treatments and prospects. *J Am Acad Psychiatry Law* 1999;27:426–42.
25. Zygmunt A, Olfson M, Boyer C, Mechanic D. Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry* 2002;159:1653–64.
26. Rittmannsberger H, Pachinger T, Kepplmuller P, Wancata J. Medication adherence among psychotic patients before admission to inpatient treatment. *Psychiatr Serv* 2004;55:174–9.
27. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J. American Psychiatric Association, Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, 2nd edition. *Am J Psychiatry* 2004;161:1–56.