Risperidone Dosing Pattern and Clinical Outcome in Psychosis: An Analysis of 1713 Cases

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Background: In treating patients with psychosis, practicing clinicians use various dosing strategies of antipsychotic medications, including risperidone. To evaluate the outcome of different risperidone dosing strategies in clinical practice, we undertook a large, prospective, naturalistic study in which daily dosage was determined freely by local standards of care.

Method: In a 6-week trial between December 2000 and January 2002, 1713 patients with DSM-IV schizophrenia and related psychoses were treated with risperidone, with the dose, daily changes in dose, and weekly changes in Brief Psychiatric Rating Scale score documented. Cluster analysis was performed to identify homogeneous dosing patterns among the heterogeneous total population.

Results: Of the 6 dosing patterns identified by cluster analysis, a 2-week titration cluster, with a starting dose of 1.8 mg/day titrated to a maximum dose of 4.7 mg/day at day 14, and a 1-week titration cluster, with a starting dose of 2.6 mg/day titrated to a maximum dose of 5.4 mg/day at day 7, showed superior clinical outcomes compared with the other clusters, in which titrations were slower and higher.

Conclusion: Our results indicate that the current consensus regarding risperidone dosing is appropriate for clinical practice, whereas a slower titration schedule does not guarantee a better clinical outcome, thus emphasizing the need for appropriate early titration.

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Compared with conventional antipsychotics, risperidone shows significant improvement in both positive and negative symptoms, without an increase in drug-induced parkinsonian symptoms at therapeutic dosages.[1] The "therapeutic dosage" was initially set at 6 mg/day,[2,3] but 4 mg/day is presently considered appropriate for most patients with schizophrenia[4] and 2 mg/day for patients with first-episode psychosis.[5] The original recommendation for dose titration was to start the patient at 2 mg/day, with increases in increments of 2 mg/day on the second and third days, to a target dose of 6 mg/day by the third day. Presently, however, slower titration is favored, in which the patient is started at 1 to 2 mg/day, with increases in increments of 0.5 to 1 mg/day, titrated over 6 or 7 days, to a target dose of 4 mg/day.[4]

Despite this consensus on optimal dosing of risperidone, a variety of dosing strategies is being practiced in real clinical settings. Data from a large inpatient pharmacy showed that a titration speed slower than that initially recommended had a better clinical outcome, as measured by a higher drug continuation rate.[6] Several studies of large numbers of patient records revealed that patients treated with target doses lower than those initially recommended had a higher discharge rate.[7,8] While these large-scale studies better reflected real clinical situations than earlier studies with rigid selection criteria and determined dosing schedules, they had the same innate problems as other retrospective studies. Discharge rate, which was used as an outcome measurement of risperidone treatment, does not adequately reflect reduction of symptoms by medication; rather, it reflects a combination of variations in physician behavior, economic state of the caretaker, or other illness factors, such as initial status of function or symptom severity. In addition, measurement of drug continuation rate is more indicative of drug tolerability than clinical outcome. Thus, it is still not known which risperidone dosing strategy would bring the most favorable drug response. Therefore, to evaluate the risperidone treatment strategies being practiced in clinical situations, a naturalistic study, which includes a heterogeneous patient population, is needed to assess the drug response by standardized symptom rating scales.[9]

We undertook a prospective naturalistic study of risperidone in a large, heterogeneous study population, in which the dosing strategies were determined freely by local standards of care, and the response to medication was assessed by the Brief Psychiatric Rating Scale (BPRS),[10] the Clinical Global Impressions (CGI) scale,[11] and the Global Assessment of Functioning scale (GAF; DSM-IV Axis V[12]). To delineate homogeneous subgroups of patients whose risperidone medication profiles could each be associated with a common dosing strategy, we introduced cluster analysis. This is a multivariate statistical procedure used to create homogeneous groups of subjects from the data, but which are not defined prior to analysis. The purpose of this study was to evaluate how and to what extent the various dosing strategies revealed by cluster analysis affect the clinical outcome of risperidone treatment. We also determined whether the current consensus about risperidone dosing is appropriate for the clinical practice.

METHOD

Subjects

Between December 2000 and January 2002, the study was conducted in 151 psychiatric centers in Korea. Included in this research project were 1713 patients diagnosed with schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, or psychotic disorder not otherwise specified (NOS), as defined in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV).[12] Of those 1713 patients, 435 patients were recruited from outpatient clinic and 1278 patients from inpatient clinic. Patients were excluded from study participation if they had current or past neurologic illness, mental retardation, or substance abuse, as evaluated by history and physical examinations. All patients gave written informed consent for participation in this study, which had been approved by the Institutional Review Board for Clinical Investigations of Asan Medical Center, Seoul, Korea.

Treatment

Patients received risperidone in a manner consistent with local standards of care. All decisions regarding medication change were made by the treatment providers. The use of concurrent antiparkinsonian drugs was permitted at any time during the study.

Assessment Parameters

Complete psychiatric and medical histories were obtained from each patient at time of entry into the study. The primary outcome parameter used in this study was the BPRS.[10] Other measures included the 7-point CGI scale[11] and the GAF[12] (DSM-IV Axis V). All measures were assessed at baseline and at 1, 3, and 6 weeks after the first visit. The safety and tolerability of risperidone were evaluated on the basis of adverse events observed by the physician or reported by the patient in response to questions about symptoms of side effects. Clinical laboratory tests were performed, as were physical examinations, an electrocardiogram, and vital sign determinations. At each visit, the occurrence of symptoms of akathisia, dystonia, dyskinesia, parkinsonism, amenorrhea, constipation, salivation, sedation, insomnia, weight gain (defined as a weight increase of ≥ 5% during the treatment), tardive dyskinesia, and neuroleptic malignant syndrome (NMS) was assessed.

Statistical Analysis

Two subpopulations were used for data analysis. The first subpopulation (noncompleters) consisted of patients who received at least 1 dose of risperidone but did not complete the study. The second population (completers) consisted of patients who took the medication for the protocol-specified 42 days and also had valid assessments on every scheduled day.

For noncompleters, missing values were imputed by the method of last observation carried forward. A paired t test was used to assess within-treatment changes from baseline to endpoint. Comparisons between the 2 subpopulations were based on analysis of variance (ANOVA) for metric scale variables (e.g., age, duration of illness) and χ^2 tests for nominal scale variables (e.g., sex, adverse events).

Cluster analysis was used to categorize different dosing strategies for the completer subpopulation. The 8 quantitative variables used to perform the cluster analysis consisted of: (1) dose on the first day, (2) dose on the last day, (3) maximum dose on at least 3 consecutive days over the 6-week treatment period, (4) number of days needed to reach the maximum dose, (5) maximum dose on at least 2 consecutive days during the first week, (6) number of days to reach that dose, (7) maximum dose on at least 2 consecutive days during the second week, and (8) number of days to reach that dose. The changes from baseline to each assessment time in BPRS total scores between clusters were examined by pairwise comparisons by ANOVA, with a significance level of 5%. Statistical analysis was performed using SAS 8e for Windows (SAS Institute Inc., Cary, N.C., 2000).

RESULTS

The mean ± SD age of the 1713 patients included in the research project was 37.6 ± 12.4 years, and about half (859, 50.1%) were female. These patients had a mean ± SD of 11.3 ± 3.6 years of education; the mean age at onset of their disorder was 29.5 ± 11.7 years, and the mean ± SD duration of illness was 6.5 ± 6.3 years. Mean age at first psychiatric hospitalization was 31.4 ± 11.3 years, and mean ± SD number of previous psychiatric hospitaliza-

Table 1. Characteristics of Total Patients and Comparison of Characteristics Between Completed and Noncompleted Cases in Study of Risperidone Dosing Pattern in Psychosis

Characteristic	Total (N = 1713)	Completers (N = 1535)	Noncompleters (N = 178)
Age, mean ± SD, y	37.6 ± 12.4	37.7 ± 12.3	36.7 ± 12.7
Sex, N (%)			
Male	854 (49.9)	786 (51.2)	68 (38.2)*
Female	859 (50.1)	749 (48.8)	110 (61.8)*
Education, mean ± SD, y	11.3 ± 3.6	11.3 ± 3.5	11.1 ± 4.1
Onset age, mean ± SD, y	29.5 ± 11.7	29.4 ± 11.7	30.2 ± 11.7
Duration of illness, mean ± SD, y	6.5 ± 6.3	6.6 ± 6.3	5.4 ± 5.9
Psychosis history, mean ± SD			
Age at first psychiatric hospitalization, y	31.4 ± 11.3	31.3 ± 11.3	32.3 ± 11.1
No. previous psychiatric hospitalizations	1.6 ± 2.1	1.7 ± 2.1	1.2 ± 2.0
Diagnosis, N (%)			
Schizophrenia	1362 (79.5)	1237 (80.6)	125 (70.2)
Schizophreniform disorder	48 (2.8)	36 (2.3)	12 (6.7)
Schizoaffective disorder	120 (7.0)	109 (7.1)	11 (6.2)
Brief psychotic disorder	44 (2.6)	36 (2.3)	8 (4.5)
Psychotic disorder NOS	139 (8.1)	117 (7.6)	22 (12.3)
Baseline score, mean ± SD			
BPRS total	59.0 ± 15.4	59.3 ± 15.4	55.9 ± 14.8*
CGI	3.9 ± 0.9	3.9 ± 0.9	3.8 ± 0.9*
GAF	34.6 ± 11.7	34.3 ± 11.6	37.7 ± 12.5*

*$p < .05$.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning scale, NOS = not otherwise specified.

tions was 1.6 ± 2.1. More than three fourths (79.5%) of the patients (N = 1362) were diagnosed with schizophrenia, 7.0% (N = 120) with schizoaffective disorder, 2.8% (N = 48) with schizophreniform disorder, 2.6% (N = 44) with brief psychotic disorder, and 8.1% (N = 139) with psychotic disorder NOS.

The completer subpopulation consisted of 1535 patients (89.6%), while the noncompleter subpopulation consisted of 178 patients (10.4%). Of the 178 noncompleters, 11 (6.2%) discontinued treatment prior to day 7, 76 (42.7%) discontinued between days 8 and 21, and 123 (69.1%) discontinued between days 22 and 42. Only 13 noncompleters (7.3%) were reported to discontinue due to adverse effects of risperidone. There were no significant differences between the total population and completer subpopulation with respect to diagnosis and sociodemographic variables, including age, sex, education level, past history of psychosis, and baseline symptom scores (Table 1). Compared with the completer population, however, the noncompleters had a significantly higher proportion of females (61.8% vs. 48.8%, $p < .05$) and milder baseline symptoms, as measured by BPRS total score (55.9 ± 14.8 vs. 59.3 ± 15.4, $p < .05$), GAF (37.7 ± 12.5 vs. 34.3 ± 11.6, $p < .05$), and CGI (3.8 ± 0.9 vs. 3.9 ± 0.9, $p < .05$).

Overall Clinical Efficacy

Last-observation-carried-forward scores for the BPRS total score were obtained for all of the 1713 original enrollees. The initial mean daily dose of risperidone was 1.9 ± 1.1 mg, increasing to a mean daily dose of 2.5 ± 1.3 mg on day 7 and 3.7 ± 1.9 mg on day 21, and stabilizing to a final daily dose of 3.9 ± 2.0 mg on day 42. The mean BPRS total score, which was 59.0 ± 15.4 at baseline, decreased to 49.9 ± 15.0 by day 7, 42.7 ± 14.1 by day 21, and 37.0 ± 13.0 by day 42, making the overall difference 20.16 ± 12.38 ($p < .001$ for each assessment time). The percent decreases in mean BPRS total score were 15.4% on day 7, 27.6% on day 21, and 37.3% on day 42. The mean CGI-Severity score at baseline was 3.9 ± 0.9, continuously decreasing to 3.3 ± 1.0 by day 7, 2.7 ± 1.0 by day 21, and 2.2 ± 1.0 by day 42, making the overall difference 1.7 ± 1.1 ($p < .001$). When we categorized patients according to their degree of improvement in BPRS total score over the course of the study, 19.3% of patients showed more than 50% improvement, 37.7% showed more than 40% improvement, 59.7% showed more than 30% improvement, and 78.4% showed more than 20% improvement.

Evaluation of Safety

The adverse events reported in the total population were parkinsonism in 330 patients (19.3%), sedation in 238 (13.9%), constipation in 200 (11.7%), acute dystonia in 78 (4.6%), weight gain in 62 (3.6%), insomnia in 41 (2.4%), amenorrhea in 37 (2.2%), salivation in 25 (1.5%), tardive dyskinesia in 23 (1.3%), and NMS in 5 (0.3%). The adverse event occurrence rate in noncompleters calculated during the observable period was not significantly different from that in completers. Although there were 5 cases of NMS throughout the study, there was no incidence of mortality. There was no report of significant changes in vital signs, blood pressure, or electrocardiogram during the course of the trial.

Analysis of Dosing Strategies

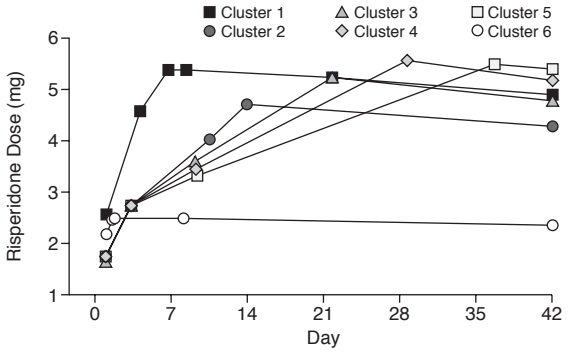
Characteristics of dosing strategy clusters. Six clusters were identified by cluster analysis (Table 2, Figure 1). Cluster 1 consisted of 400 patients with a mean ± SD starting dose of 2.6 ± 1.4 mg/day, the highest among the 6 clusters. Titration speed of this cluster was also the fastest, with a maximum dose of 5.4 ± 1.4 mg/day reached after 6.6 ± 2.5 days, leading us to label it the "1-week titration group." Clusters 2, 3, 4, and 5 differed with respect to titration speed and maximal dosages. Cluster 2, con-

Table 2. Means and Standard Deviations for 6 Risperidone Dosing Strategy Clusters

Variable	Cluster 1 (N = 400)	Cluster 2 (N = 340)	Cluster 3 (N = 211)	Cluster 4 (N = 128)	Cluster 5 (N = 106)	Cluster 6 (N = 350)
Dose at day 1, mg/d	2.58 ± 1.35	1.75 ± 0.78	1.69 ± 0.93	1.78 ± 0.99	1.79 ± 0.88	2.17 ± 1.03
Dmax1, mg/d	4.57 ± 1.61	2.74 ± 1.21	2.82 ± 1.43	2.71 ± 1.35	2.67 ± 1.41	2.47 ± 1.07
Days to Dmax1	4.11 ± 2.20	3.40 ± 2.34	3.47 ± 2.35	3.13 ± 2.26	2.92 ± 2.25	1.67 ± 1.41
Dmax2, mg/d	5.40 ± 1.46	4.04 ± 1.65	3.61 ± 1.53	3.48 ± 1.53	3.34 ± 1.61	2.48 ± 0.99
Days to Dmax2	8.31 ± 0.78	10.41 ± 2.22	9.07 ± 1.78	9.11 ± 1.89	9.23 ± 1.87	8.01 ± 0.27
MD, mg/d	5.40 ± 1.44	4.71 ± 1.70	5.23 ± 1.79	5.56 ± 1.83	5.50 ± 2.08	2.52 ± 0.98
Days to MD	6.64 ± 2.45	13.72 ± 2.08	21.32 ± 1.81	28.37 ± 1.99	36.16 ± 2.13	2.18 ± 2.16
Dose at day 42, mg/d	4.89 ± 1.58	4.27 ± 1.62	4.76 ± 1.76	5.18 ± 1.85	5.41 ± 2.10	2.34 ± 1.03

Abbreviations: Dmax1 = maximum dose on at least 2 consecutive days during the first week, Dmax2 = maximum dose on at least 2 consecutive days during the second week, MD = maximum dose on at least 3 consecutive days during the 6-week treatment period.

Figure 1. Risperidone Dosing Pattern in a 6-Week Trial Using 6 Dosing Clusters[a]



[a]Five anchoring points in each cluster were composed of 8 variables: dose on the first day, maximum dose on at least 2 consecutive days during the first week, number of days required to attain that dose, maximum dose on at least 2 consecutive days during the second week, number of days required to attain that dose, maximum dose on at least 3 consecutive days during the 6-week treatment period, number of days required to attain maximum dose, and dose on the last day.

sisting of 340 patients, had a maximum dose of 4.7 ± 1.7 mg/day at 13.7 ± 2.1 days; cluster 3, consisting of 211 patients, had a maximum dose of 5.2 ± 1.8 mg/day at 21.3 ± 1.8 days; cluster 4, consisting of 128 patients, had a maximum dose of 5.6 ± 1.8 mg/day at 28.4 ± 2.0 days; and cluster 5, consisting of 106 patients, had a maximum dose of 5.5 ± 2.1 mg/day at 36.1 ± 2.1 days. In these 4 clusters, the maximum dose increased as the days to the maximal dose increased, leading us to label these clusters as the "2-week titration group," "3-week titration group," "4-week titration group," and "5-week titration group," respectively. Cluster 6, which consisted of 350 patients, had a distinctively different dosing strategy from the other clusters. Patients in this cluster started at a dose of 2.2 ± 1.0 mg/day and reached a maximal dose of 2.5 ± 1.0 mg/day in 2.2 ± 2.2 days, which was the lowest maximum dose among the 6 clusters. Patients in this cluster maintained this dose, reaching 2.3 ± 1.0 mg/day at 42 days, leading us to label this cluster the "low-dose maintenance group."

Changes in total BPRS scores by cluster. With the exception of cluster 6, the baseline BPRS scores did not differ significantly by cluster (Table 3, Figure 2). Cluster 6, however, had significantly lower BPRS scores than the other clusters ($p < .05$). At day 21, cluster 2 had significantly lower BPRS scores than the other clusters, except for cluster 1. At day 42, the mean BPRS score of cluster 6 was significantly lower than that of the other clusters, and the mean BPRS scores differed significantly from each other, except between adjacent clusters. Clusters 1 and 2 experienced the greatest changes in mean BPRS score over the 42 days of treatment ($p < .0001$), followed by clusters 6, 3, 4, and 5, in that order. When we determined the onset of therapeutic effects by cluster for clusters 1 through 5, we found that clusters 1 and 2 were favored over the others, starting at day 21 and continuing until day 42 ($p < .001$).

Analysis of adverse events by cluster. The adverse events and their frequency of occurrence among the 6 clusters are presented in Table 4. There were no significant differences in the occurrence of adverse events among the 6 clusters.

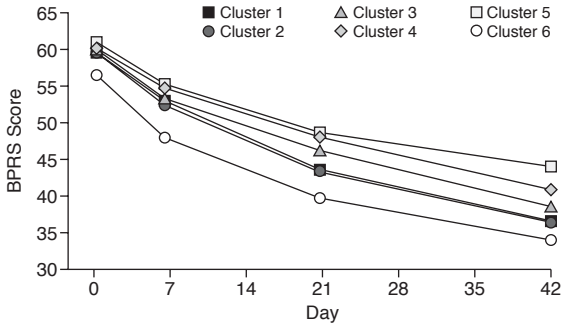
Sociodemographic characteristics by cluster. Except for cluster 6, all clusters had similar sociodemographic characteristics (Table 4). The ratio of outpatients to inpatients, mean age, years of education, age at onset, and age at first psychiatric hospitalization were similar in clusters 1 through 5, as were the percentages of each cluster by sex, diagnosis, and the case of first episode. Patients in cluster 6, however, had significantly higher mean age and age at first hospitalization than patients in the other 5 clusters, and the age at onset in cluster 6 was significantly higher than in clusters 1 through 4. In addition, the makeup of cluster 6 by diagnosis was significantly different from that of the other clusters. In cluster 6, the proportion of patients with schizophrenia was lower, while the proportions of patients with nonschizophrenic psychosis, including schizoaffective disorder, brief psychotic disorder,

Table 3. Means and Standard Deviations of Brief Psychiatric Rating Scale Total Scores for 6 Risperidone Dosing Clusters[a,b]

Assessment Point	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Baseline	61.0 ± 16.4*	59.3 ± 14.5*	59.5 ± 15.3*	60.1 ± 14.5*	61.1 ± 15.6*	56.4 ± 15.3†
Wk 1	52.8 ± 15.7*	52.2 ± 14.4*	53.0 ± 14.6*	54.4 ± 14.0*	55.3 ± 16.1*	48.0 ± 14.4†
Wk 3	43.8 ± 15.4*†‡	43.5 ± 13.8*	46.2 ± 13.1†‡§	48.0 ± 13.8‡§	48.7 ± 15.7§	39.7 ± 13.1‖
Wk 6	36.6 ± 13.5*†	36.4 ± 13.6*†	38.4 ± 12.8†‡	40.9 ± 12.5‡§	44.1 ± 14.4§	34.1 ± 11.7‖

[a]Means in the same row with totally different symbols differ significantly ($p < .05$).
[b]Across all clusters, all means in the same column during 6 weeks differ significantly (at least $p < .01$ for each assessment point).

Figure 2. Changes in Brief Psychiatric Rating Scale (BPRS) Total Scores by Risperidone Dosing Cluster[a]



[a]Cluster 1 and cluster 2 demonstrated similar response patterns with faster ($p < .001$) and greater change of mean BPRS total score during 42 days compared with other clusters ($p < .0001$).

and psychotic disorder NOS, were higher than in the other clusters.

DISCUSSION

In the present trial, which permitted a free dosing schedule in a large number of patients, we found that 6 weeks of treatment with risperidone resulted in significant improvements from baseline on BPRS total score, from 59.0 to 37.0, and CGI-Severity score, from 3.9 to 2.2, indicating that risperidone induces an improvement from moderate-severe to mild-moderate illness. After treatment, 78.4% of patients showed more than 20% improvement in BPRS total score, a finding consistent with previous reports.[13] The mean risperidone dosage of the total population at 3 weeks was 3.7 mg/day, which was stably maintained at 3.9 mg/day after 6 weeks. Although these data suggest that clinicians generally followed the consensus target dosage of risperidone (4 mg/day), cluster analysis by dosing pattern revealed other results.

From the completer population of 1535 patients, 6 different dosing strategies were identified. Cluster 1 started at about 2.6 mg/day, reaching a maximum dose of 5.4 mg/day within 1 week. Clusters 2, 3, 4, and 5 shared common features. These 4 clusters started at about 1.7 mg/day and reached about 2.7 mg/day after 1 week. Differences became manifest during the second week and thereafter. Cluster 2 reached its maximal dose at the end of the second week, cluster 3 at the end of the third week, cluster 4 at the end of the fourth week, and cluster 5 at the end of the fifth week. In contrast, cluster 6 had no titration period, since these patients started with 2.2 mg/day and ended at 6 weeks with 2.3 mg/day. Cluster analysis thus shows that the target dose in clusters 1 through 5 was 5 mg/day, whereas that of cluster 6 was 2 mg/day. Patients in cluster 6 had milder psychotic symptoms than those of the other clusters; therefore, the risperidone dose for major psychosis seems to be slightly higher and its titration speed slightly slower than the consensus target dose of 4 mg/day over 6 or 7 days.

The relationship between cluster membership and clinical outcome showed a distinct pattern. In all 6 clusters, significant reductions in the severity of symptoms of psychosis were seen after 1 week of treatment, and further improvements were noted throughout the 6-week trial. The degree of improvement, however, differed among the clusters. The greatest reduction in symptoms was observed in clusters 1 and 2, and these reductions were significantly larger than those in clusters 3, 4, and 5. Among clusters 2, 3, 4, and 5, the degree of symptom reduction differed significantly only between nonadjacent clusters; for example, cluster 2 showed significantly larger symptom reduction than clusters 4 and 5, and cluster 3 showed significantly larger symptom reduction than cluster 5. Interestingly, the cluster order by dosing pattern was preserved in the degree of symptom reduction. In contrast to the other 5 clusters, cluster 6 had a significantly lower baseline BPRS total score, as well as different sociodemographic characteristics, including higher mean age, age at onset, and age at first admission, a lower proportion of patients with schizophrenia, and a higher proportion of patients with other psychoses, indicating that the patients in cluster 6 had milder psychotic symptoms than those in the other clusters. From the observation that clusters 1 and 2 showed best clinical outcome, without differing from the other clusters with respect to baseline symptoms, sociodemographic characteristics, and occurrence of adverse events, we could confirm that a titration speed

Table 4. Sociodemographic Characteristics and Side Effect Profile of 6 Risperidone Dosing Clusters

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Subjects, N (%)	400 (26)	340 (22)	211 (14)	128 (8)	106 (7)	350 (23)
Outpatient/inpatient ratio, mean ± SD	134 ± 266	82 ± 258	46 ± 165	34 ± 94	28 ± 78	65 ± 285
Age, mean ± SD, y	36.9 ± 10.8	37.2 ± 12.4	35.9 ± 11.6	36.4 ± 12.8	37.7 ± 12.8	40.6 ± 13.6*
Sex, N (%)						
Male	213 (53)	170 (50)	126 (60)	62 (48)	54 (51)	161 (46)
Female	187 (47)	170 (50)	85 (40)	66 (52)	52 (49)	189 (54)
Education, mean ± SD, y	11.6 ± 3.4	11.5 ± 3.4	11.6 ± 3.3	11.5 ± 3.2	11.8 ± 3.3	10.5 ± 3.8
Diagnosis, N (%)						
Schizophrenia	350 (88)	274 (81)	173 (82)	111 (87)	89 (84)	240 (69)*
Schizophreniform disorder	10 (3)	5 (1)	9 (4)	2 (2)	2 (2)	8 (2)
Schizoaffective disorder	20 (5)	25 (7)	12 (6)	9 (7)	5 (5)	38 (11)*
Brief psychotic disorder	7 (2)	10 (3)	3 (1)	1 (1)	1 (1)	14 (4)*
Psychotic disorder NOS	13 (3)	26 (8)	14 (7)	5 (4)	9 (8)	50 (14)*
Onset age, mean ± SD, y[a]	28.9 ± 10.3†	29.0 ± 10.5†	27.9 ± 10.7†	28.5 ± 12.9†	29.5 ± 13.5†‡	31.9 ± 13.5‡
Illness duration, mean ± SD, y	6.7 ± 6.1	6.2 ± 5.8	6.4 ± 5.9	7.5 ± 8.3	6.9 ± 6.4	6.8 ± 6.5
Psychosis history						
First episode, N (%)	101 (25)	95 (28)	64 (30)	34 (27)	30 (28)	80 (23)
Age at first psychiatric hospitalization, mean ± SD, y	30.3 ± 10.4	31.4 ± 10.7	29.7 ± 11.4	30.8 ± 10.4	31.6 ± 11.5	34.2 ± 2.7*
No. previous psychiatric hospitalizations, mean ± SD	1.9 ± 2.4	1.5 ± 2.0	1.5 ± 2.0	1.6 ± 1.9	1.6 ± 2.2	1.7 ± 2.1
No. previous antipsychotic medications, mean ± SD	1.3 ± 1.2	1.1 ± 1.1	1.2 ± 1.2	1.2 ± 1.1	1.2 ± 1.2	1.2 ± 1.1
Drug side effect, N (%)						
Parkinsonism	73 (18)	82 (24)	44 (21)	26 (20)	40 (38)	42 (12)
Sedation	58 (15)	49 (14)	26 (12)	15 (12)	24 (23)	47 (13)
Constipation	66 (17)	41 (12)	21 (10)	13 (10)	20 (19)	18 (5)
Acute dystonia	21 (5)	17 (5)	9 (4)	7 (6)	3 (3)	9 (3)
Weight gain	11 (3)	11 (3)	9 (4)	7 (6)	9 (9)	11 (3)
Insomnia	9 (2)	8 (2)	7 (3)	1 (1)	7 (7)	8 (2)
Amenorrhea	10 (3)	6 (2)	0 (0)	2 (2)	4 (4)	10 (3)
Salivation	4 (1)	1 (< 1)	4 (2)	1 (1)	5 (5)	5 (1)
Tardive dyskinesia	7 (2)	3 (1)	1 (1)	1 (1)	2 (2)	3 (1)
Neuroleptic malignant syndrome	1 (< 1)	0 (0)	0 (0)	1 (1)	3 (3)	0 (0)

[a]Means with totally different symbols differ significantly ($p < .05$).
*$p < .05$.
Abbreviation: NOS = not otherwise specified.

slower than that requiring more than 2 weeks to reach maximum dose was not associated with better clinical outcome. These results suggest that the titration speed of 0.5-mg increase per day can be a good guidance of dosing strategy of risperidone treatment. The magnitude of difference in the maximum or final dose was not to such a degree as to be clinically significant between cluster 1, 2 and cluster 4, 5; also, the difference in outcome began to be noticed at 2 weeks during the 6 weeks of treatment. These findings indicate that the better clinical outcome in clusters 1 and 2 compared with clusters 4 and 5 seems to be related to differences in titration speed rather than differences in maximal or final dosage.

There can be an argument that the dosing strategy may be a result rather than a cause of treatment outcome. Unlike planned dosing strategy in controlled studies, the dosing strategy in natural clinical practice can be continuously modified by the treatment response; therefore, the slower up-titration in the case of clusters 4 and 5 might be the result rather than the cause of poorer drug response. This might explain the differences in dosing strategies between cluster 4, 5 and cluster 6. In clusters 4 and 5, the dosage was raised slowly as the treatment response was not satisfactory, while the dosage remained almost constant in cluster 6 with milder psychotic symptoms. However, the better outcome in clusters 1 and 2 compared with clusters 4 and 5 could be accounted for by faster titration because there was no significant difference with respect to baseline clinical and sociodemographic characteristics among clusters.

Naturalistic studies have an advantage over controlled clinical trials, in that the former offer important insights into everyday clinical practice.[14] Specifically, naturalistic studies have a low risk of the selection bias imposed by specific inclusion and exclusion criteria in controlled clinical trials. However, naturalistic studies have an innate drawback in that they are vulnerable to the criticism of being just larger case reports, because the included subjects are generally heterogeneous with respect to the characteristics sought by the investigators. In addition, our study had an additional drawback regarding the heterogeneity of dosing strategy in the study population. To circumvent this problem, we used cluster analysis, which was expected to solve the problem of heterogeneity be-

cause it can extract homogeneous groups of subjects from a larger, heterogeneous population. The effectiveness of our cluster analysis was confirmed by showing that the 6 different dosing patterns resulted in different clinical outcomes. Cluster analysis, in which groups of subjects are subtyped based on their symptoms profiles[15] or on response to medication,[16] has a proven record in the field of psychiatry. We believe that the methodological aspects presented in this article can be used as an effective approach in analyzing the data from a large, prospective, naturalistic clinical trial.

As one of the limitations of the study, we can notice a small magnitude of difference in the clinical improvement among clusters. Although it was significant statistically, the difference in BPRS scores between the highest symptom reduction group and lowest symptom reduction group was not so large, about 7.3 points. That might be the minimum difference that can be considered clinically significant. A large number of subjects in the present study enabled us to detect this small effect of dosing strategies on the treatment outcome, which might be easily obscured by various confounding factors, such as treatment milieu, premorbid adjustment, symptomatology, etc.[17,18] Since the parameters we referenced to separate the clusters were only about the factors of dosing schedule, ignoring all other factors that might affect clinical outcome, the pure influence of dosing schedule on the clinical outcome might not be as large as we expected.

The results should be cautiously extended to other Asian or Caucasian populations. In the study of interethnic differences in efficacy of clozapine, Koreans with schizophrenia, as compared to Caucasians, required lower doses of clozapine to obtain similar levels of efficacy.[19] Similar results were noted in Asian males compared with Caucasian males at a fixed dose of haloperidol.[20]

In conclusion, by recruiting a large number of patients and using cluster analysis, we evaluated the clinical outcome of various risperidone dosing strategies in real clinical situations. The similar epidemiologic characteristics and initial symptom scores observed among the clusters suggest that different dosing patterns result in different clinical outcomes. These findings suggest that the current consensus about risperidone titration speed is appropriate for clinical practice, whereas slower titration does not guarantee better clinical outcome, thus emphasizing the need for appropriate early titration.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), risperidone (Risperdal).

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