Effects of Changing From Typical to Atypical Antipsychotic Drugs on Subjective Sleep Quality in Patients With Schizophrenia in a Japanese Population

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Objective: To investigate the effects of the atypical antipsychotic drugs risperidone, olanzapine, quetiapine, and perospirone on the subjective quality of sleep in patients with schizophrenia.

Method: Subjects were 92 inpatients (mean age = 59.9 years) who had been receiving treatment with conventional antipsychotic drugs and who met the DSM-IV criteria for schizophrenia. Subjects were randomly assigned to receive 1 of 4 atypical antipsychotic drugs (olanzapine, perospirone, quetiapine, and risperidone). Subjective sleep quality and psychopathology were assessed twice: at baseline and 8 weeks after switching. Data were collected from June 2001 to December 2001. Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI), and psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS).

Results: Subjective sleep quality as assessed by the PSQI was significantly improved with administration of olanzapine, risperidone, or quetiapine, but not with perospirone, in comparison with conventional antipsychotic drugs. Multiple regression analysis revealed that the improvement of sleep quality with administration of atypical antipsychotic drugs was predicted by poor sleep quality at baseline. In addition, improvement of sleep quality was significantly correlated with improvement of negative symptoms as assessed by the PANSS.

Conclusion: These results demonstrated that atypical antipsychotic drugs improved subjective quality of sleep in patients with schizophrenia compared with conventional antipsychotic drugs, suggesting that the marked potency of serotonin-2 receptor blockade in atypical antipsychotic drugs may be involved in the mechanism of this improvement. These improvements were correlated with improvement of negative symptoms.

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One of the major symptoms of schizophrenia is sleep disturbance. Deterioration of sleep, such as prolongation of sleep latency, shortening of total sleep time, and a decrease in sleep efficiency, has been reported in patients with schizophrenia.[1] In addition, a decrease in the duration of slow wave sleep (SWS)[2] and shortened rapid eye movement (REM) latency with relatively normal REM time and density[2,3] have been demonstrated.

Sleep disturbance may exacerbate existing psychopathology by causing distress and negatively affecting general functioning in patients with schizophrenia. Decreased SWS was reported to be associated with impairment of cognitive function[4] and negative symptoms.[5] Treatment of sleep disturbance may contribute to improved quality of life in patients with schizophrenia.

Investigations of the effects of conventional antipsychotic drugs have shown that these agents could improve sleep continuity, sleep duration, and REM abnormalities, but not SWS.[6–8] The effects on sleep of atypical antipsychotic drugs could be expected to differ from those of typical antipsychotic drugs because of differences in their pharmacologic profiles. Recent pharmacologic studies of sleep revealed the importance of serotonin-2A/2C (5-$HT_{2A/2C}$) receptors on sleep quality. For example, a selective 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, was reported to increase SWS in healthy volunteers[9,10] and in patients with dysthymia.[11]

Table 1. Characteristics of Schizophrenia Patients Switched From Typical to Atypical Antipsychotics

Characteristic	Total	Olanzapine	Risperidone	Perospirone	Quetiapine	p Value[b]
Age, y	59.9 ± 10.5	56.2 ± 11.2	62.8 ± 9.8	59.2 ± 8.6	61.0 ± 11.3	.22
Range	28 to 84	28 to 84	44 to 79	43 to 74	38 to 83	
Sex, male/female, N	48/44	11/9	9/11	15/9	13/15	.60
Periods of morbidity, y	34.0 ± 9.5	32.6 ± 8.7	37.6 ± 10.2	32.5 ± 9.2	33.7 ± 9.2	.26
Range	9.1 to 54.0	9.1 to 54.0	19.4 to 53.3	12.2 to 49.1	11.9 to 47.7	
Schizophrenia type, N						
Disorganized	29	7	9	2	11	.16
Paranoid	11	3	2	4	2	
Undifferentiated	52	10	9	18	15	
Dose, mean ± SD, mg/d[a]	1137 ± 981	1466 ± 984	917 ± 776	961 ± 739	1209 ± 1194	.25
Range	50 to 4383	80 to 3362	100 to 2425	88 to 3637	50 to 4383	
PSQI baseline total score, mean ± SD	8.6 ± 3.8	9.5 ± 3.0	9.1 ± 4.2	7.9 ± 3.0	8.2 ± 3.5	.47
Range	0 to 17	0 to 16	1 to 17	3 to 16	1 to 16	
PANSS baseline total score, mean ± SD	81.1 ± 15.2	82.8 ± 12.2	80.9 ± 12.9	75.1 ± 11.4	85.2 ± 19.5	.11
Range	50 to 120	60 to 108	53 to 102	54 to 109	50 to 120	
PANSS total score change, mean ± SD	–8.3 ± 7.0*	–8.3 ± 7.0*	–6.2 ± 4.7*	+2.6 ± 11.9	–4.0 ± 6.7*	
Range	–21 to 56	–21 to 2	–20 to 0	–7 to 56	–17 to 10	

[a]Converted to chlorpromazine equivalent dosage.
[b]For categorical variables (sex and type of disease), p values were obtained with the χ^2 test; for numerical variables, p values were obtained with analyses of variance.
*p < .01 compared with baseline; obtained with paired t test.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, PSQI = Pittsburgh Sleep Quality Index.

To date, there have been several studies on the effect of atypical antipsychotic drugs on sleep. Previously, Dursun and coworkers[12] demonstrated better sleep quality in patients with schizophrenia who were treated with risperidone compared with patients receiving typical antipsychotic drugs. We reported a longer duration of SWS in patients with schizophrenia treated with risperidone than in those treated with haloperidol.[13] Acute administration of olanzapine was reported to increase sleep efficiency and SWS in drug-free patients with schizophrenia[14] and in healthy volunteers.[15] In addition, Lee and associates[16] reported that clozapine improved the continuity of sleep in schizophrenia. However, the effect of atypical antipsychotic drugs on sleep has not been compared with that of typical conventional antipsychotic drugs in the same patients with schizophrenia.

In this context, to evaluate the effect of atypical antipsychotic drugs on sleep, we compared sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) in patients with schizophrenia while they were receiving typical conventional antipsychotic drugs and after they had been prescribed atypical antipsychotic drugs.

METHOD

Subjects

Subjects were 92 inpatients (48 men and 44 women) who had been taking conventional antipsychotic drugs only and who fully met the DSM-IV criteria for schizophrenia.[17] This study was designed in accordance with institutional guidelines and was approved by an institutional review committee. The subjects were fully informed of the purpose and procedures of the study; each subject gave written informed consent prior to enrollment. Patients were excluded if they had a severe physical illness based on results of clinical, laboratory, and imaging evaluations; a cerebral organic disease; or a history of alcoholism, drug abuse, or neurologic illness. Prior to enrollment in the study, subjects underwent medical and psychiatric screening to ensure they had no underlying cause of sleep disturbance, such as sleep apnea or restless legs syndrome. Patients who received a depot antipsychotic within 4 weeks of randomization were also excluded. Three patients had received a depot antipsychotic drug (haloperidol decanoate) before this study.

The mean age of the study population was 59.9 years (SD = 10.5, range = 28–84), and the mean duration of illness was 34.0 years (SD = 9.5, range = 9.1–54.0). The mean daily dosage of antipsychotic drug was 1137 mg/day (SD = 981, range = 50–4383) expressed as the chlorpromazine equivalent (Table 1). The mean number of antipsychotics administered at baseline was 2.2 (SD = 1.1, range = 1.0–5.0); the most common drugs were haloperidol (N = 64, 70%), chlorpromazine (N = 39, 42%), and levomepromazine (N = 23, 25%).

Treatments

After completing baseline assessments, subjects were randomly assigned to receive 1 of 4 atypical antipsychotic drugs: olanzapine (N = 20), perospirone (N = 24), quetiapine (N = 28), or risperidone (N = 20). Perospirone is a newer atypical antipsychotic agent for the treatment of schizophrenia that was developed in Japan. It was shown to have a better effect on negative symptoms and a similar effect on general and positive symptoms compared with haloperidol in phase II and phase III trials.[18]

At the time of switching, the dose of ongoing typical antipsychotics was tapered, and finally all typical antipsy-

Table 2. Change in Pittsburgh Sleep Quality Index Score and Other Sleep Variables in Schizophrenia Patients Switched From Typical to Atypical Antipsychotic Treatment[a]

Variable	Baseline	Second Assessment	t Score	p Value[b]
Total score	8.58 ± 3.80	7.20 ± 4.29	3.246	.002
Subscores				
Sleep quality	1.12 ± 0.76	0.87 ± 0.87	2.305	.023
Sleep latency	1.72 ± 1.26	1.31 ± 1.26	3.090	.003
Sleep duration	0.60 ± 0.90	0.54 ± 0.94	0.565	.574
Habitual sleep efficiency	0.88 ± 1.06	0.56 ± 0.97	2.504	.014
Sleep disturbances	0.82 ± 0.53	0.69 ± 0.49	2.009	.047
Use of sleep medications	2.28 ± 1.26	2.27 ± 1.29	0.695	.488
Daytime dysfunction	1.16 ± 0.64	0.97 ± 0.59	2.473	.015
Other sleep variables				
Time in bed, min	540.1 ± 53.2	516.0 ± 47.9	3.667	.004
Total sleep time, min	441.5 ± 89.1	446.5 ± 86.3	0.477	.634
Sleep latency, min	54.7 ± 58.1	38.4 ± 50.2	2.410	.018
Sleep efficiency, %	81.8 ± 14.9	86.5 ± 14.6	2.541	.012

[a]Values are mean ± SD.
[b]p Values were obtained with paired t test.

chotics were discontinued over a period of 4 weeks. During this tapering period, 1 of the 4 atypical antipsychotic drugs was started, and its dosage was increased gradually. The target dose of atypical antipsychotic drugs was determined from the dose of ongoing typical antipsychotic drugs. After completion of switching, a psychiatrist adjusted dosages depending on the subject's clinical status. During the study, the antipsychotic dose was allowed to vary within the following ranges: olanzapine, 2.5 to 20.0 mg/day; perospirone, 4.0 to 48.0 mg/day; quetiapine, 50.0 to 750.0 mg/day; and risperidone, 1.0 to 12.0 mg/day. Mean dose levels at endpoint were 16.5 mg/day for olanzapine, 37.3 mg/day for perospirone, 432.5 mg/day for quetiapine, and 7.4 mg/day for risperidone.

Sixty-three percent of the subjects received hypnotics, 29% received anxiolytics, 20% received mood stabilizers, and 4% received antidepressants. These concomitant medications were not changed during the study.

Assessment of Quality of Sleep and Psychopathology

Subjective sleep quality and psychopathology were assessed at 2 intervals: baseline and 8 weeks after the switching was completed. We used the PSQI[19] to assess subjective sleep quality. The PSQI is a self-administered questionnaire to assess subjective sleep quality during the previous month. The self-rated items on the PSQI generate 7 subscale scores, each ranging from 0 to 3: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The sum of these 7 component scores yields 1 global score of subjective sleep quality ranging from 0 to 21, with higher scores representing poorer subjective sleep quality. The Positive and Negative Syndrome Scale (PANSS)[20] was used to rate schizophrenia symptoms. Data were collected from June 2001 to December 2001.

Data Analysis

Before analyzing sleep quality data, we examined demographic variables of each treatment group with analyses of variance (ANOVA) and the χ^2 test. The PSQI total score and each subscale score of the PSQI were compared before and after switching to atypical antipsychotic drugs. These comparisons were performed using a paired t test for all subjects. One-way ANOVA was conducted to compare the PSQI change scores in the 4 medication groups. The Fisher protected least significant difference test was performed for post hoc comparison. Multiple regression analysis was used to investigate the factors that predict improvement of sleep quality with atypical antipsychotic drug treatment. Change in PSQI total scores was entered into the analysis as a dependent variable. Demographic variables, the total PANSS score, subjective sleep quality, and the chlorpromazine-equivalent dosage of antipsychotic drugs at baseline were entered as independent variables for all subjects. The relationships between the PSQI total scores and the PANSS positive, negative, general, and total scores were investigated by Pearson correlation analysis. In addition, the relationships between changes in PSQI total scores and changes in PANSS positive, negative, general, and total scores were investigated. The results are expressed as means ± standard deviations, and significance was set at $p < .05$.

RESULTS

Demographic and clinical characteristics of the 92 patients are shown in Table 1. No statistically significant difference was detected among the 4 groups in age, distribution by sex, or duration of illness. Neither were there differences in baseline severity of psychopathology as assessed by the PANSS, subjective sleep quality as assessed by the PSQI, or chlorpromazine-equivalent dosages of antipsychotic drugs. Of the patients treated with perospirone, 1 dropped out before the second assessment because of worsening of psychotic symptoms. Of the patients treated with quetiapine, 1 dropped out before the second assessment because of hip fracture. All patients treated with olanzapine and risperidone completed the study protocol.

Changes in the PSQI total score and each subscale score with administration of the atypical antipsychotic drugs are shown in Table 2. Compared with conventional antipsychotic drugs, subjective sleep quality as assessed using the PSQI total score was significantly improved. As for the PSQI subscores, sleep quality, sleep latency, habitual sleep efficiency, sleep disturbance, and daytime dysfunction were improved, but sleep duration and use of sleep medication did not change in the total patient popu-

Table 3. Pittsburgh Sleep Quality Index Change in Score in Schizophrenia Patients Switched From Typical to Atypical Antipsychotics

Score	Olanzapine	Perospirone	Quetiapine	Risperidone	F Value	p Value[a]
Total	–3.20 ± 3.95**	1.56 ± 4.01	–1.93 ± 4.19**	–2.45 ± 2.89**	6.714	.0004
Subscale						
Sleep quality	–0.50 ± 1.15	0.22 ± 0.85	–0.33 ± 0.87	–0.35 ± 0.88	2.521	.063
Sleep latency	–0.45 ± 1.43	–0.22 ± 1.17	–0.59 ± 1.28	–0.35 ± 1.23	0.380	.76
Sleep duration	–0.55 ± 1.10**	0.69 ± 1.14	–0.22 ± 0.93**	–0.25 ± 0.97**	6.018	.0009
Habitual sleep efficiency	–0.80 ± 1.11**	0.47 ± 1.20	–0.44 ± 1.28**	–0.65 ± 1.18**	5.212	.0024
Sleep disturbances	–0.20 ± 0.62	0.04 ± 0.56	–0.11 ± 0.42	–0.25 ± 0.71	1.086	.36
Use of sleep medications	–0.05 ± 0.22	0.13 ± 1.10	–0.07 ± 1.04	–0.30 ± 0.92	0.796	.50
Daytime dysfunction	–0.65 ± 0.75**	0.21 ± 0.67	–0.15 ± 0.82*	–0.30 ± 0.57*	5.418	.0018

[a]p Values were obtained with analyses of variance. Fisher test was performed for post hoc comparison.
*p < .05 compared with perospirone.
**p < .01 compared with perospirone with Fisher test.

Table 4. Multiple Regression Analysis of Factors Predicting Improvement of PSQI Score in Schizophrenia Patients Switched From Typical to Atypical Antipsychotics[a]

Variable	Coefficient	SE	Standardized Coefficient	t Score	p Value
Sex	0.242	0.929	0.029	0.260	.79
Age	–0.018	0.055	–0.046	0.329	.74
Illness duration	0.003	0.005	0.078	0.574	.56
Schizophrenia type (undifferentiated)[b]					
Disorganized	–0.609	1.029	–0.068	0.592	.56
Paranoid	0.528	1.385	0.041	0.381	.70
Baseline antipsychotic drugs[c]	0.0002	0.0004	0.046	0.429	.67
Baseline PANSS total score	0.012	0.032	0.044	0.380	.71
Baseline PSQI total score	–0.462	0.118	–0.423	3.923	.0002

[a]$R^2 = 0.194$; adjusted $R^2 = 0.115$.
[b]For the categorical variables, the first type (undifferentiated) was used as the reference category.
[c]Converted to chlorpromazine equivalent dosage.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, PSQI = Pittsburgh Sleep Quality Index.

lation. Some actual sleep variables are shown in Table 2. Time in bed and sleep latency were shortened, and sleep efficiency was improved with administration of the atypical antipsychotic drugs.

An overall difference in efficacy among the 4 atypical antipsychotic drugs was observed (Table 3). Olanzapine, risperidone, and quetiapine were superior to perospirone in their improvement of the PSQI total score, sleep duration, habitual sleep efficiency, and daytime dysfunction.

Multiple regression analysis revealed that the improvement of subjective sleep quality with administration of atypical antipsychotic drugs was predicted by poor sleep quality at baseline (Table 4). The correlation between subjective sleep quality and the severity of psychotic symptoms was insignificant at baseline (Table 5); however, the improvement of subjective sleep quality was significantly correlated with improvement of negative symptoms as assessed by the PANSS (Table 6).

DISCUSSION

While there are several reports on the effect of atypical antipsychotic drugs on sleep quality in patients with schizophrenia, to our knowledge, no previous report has compared the effect of atypical antipsychotic drugs on sleep quality with that of typical conventional antipsychotic drugs in the same group of patients with schizophrenia. This appears to be the first such study.

The present study demonstrated that, when compared with conventional antipsychotic drugs, subjective sleep quality as assessed by the PSQI was significantly improved in the study patients with schizophrenia after administration of olanzapine, risperidone, or quetiapine. No improvement was noted with perospirone. Also, improvement of subjective sleep quality after change in treatment was predicted by poor sleep quality at baseline and also was significantly correlated with improvement of negative scores on the PANSS.

The reason for the improvement of sleep disturbances with atypical antipsychotic drugs compared with typical conventional antipsychotic drugs has been postulated to be due to the higher potency of 5-HT_2 receptor blockade. It has been reported that a selective 5-HT_2 (5-HT_{2A} < 5-HT_{2C}) receptor antagonist, ritanserin, increases the duration of SWS in rats,[21,22] healthy volunteers,[9,10] and patients with dysthymia.[11] Olanzapine has a high affinity for both 5-HT_{2A} and 5-HT_{2C} receptors and caused an increase of SWS in healthy volunteers[15] and in drug-free patients with schizophrenia.[14] In contrast, the 5-HT_{2C} agonist, meta-chlorophenylpiperazine (m-CPP), was reported to decrease SWS in healthy volunteers.[23,24] The amount of SWS and sleep continuity predict subjec-

Table 5. Correlations Between PSQI Total Scores and PANSS Scores at Baseline in Schizophrenia Patients Switched From Typical to Atypical Antipsychotics

	PSQI Total Scores	
PANSS Scores	r Value	p Value[a]
Positive	0.120	.253
Negative	–0.074	.485
General	0.084	.424
Total	0.058	.584

[a]p Values were obtained with Pearson correlation analysis.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, PSQI = Pittsburgh Sleep Quality Index.

Table 6. Correlations Between Change in PSQI Total Scores and Change in PANSS Scores (baseline to follow-up) in Schizophrenia Patients Switched From Typical to Atypical Antipsychotics

	Change in PSQI Total Scores	
Change in PANSS Scores	r Value	p Value[a]
Positive	0.200	.083
Negative	0.254	.026
General	0.001	.999
Total	0.147	.206

[a]p Values were obtained with Pearson correlation analysis.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, PSQI = Pittsburgh Sleep Quality Index.

tive quality of sleep.[25,26] In this context, it is conceivable that the blockade of 5-HT_2 receptors may be associated with the regulation of sleep quality by increasing SWS. These findings suggest that the potent 5-HT_2 receptor blockade may be closely involved in the improvement of sleep quality shown in this study.

Another possible explanation is that the difference in sedative effect between conventional and atypical antipsychotic drugs improved the subjective quality of sleep. Wirz-Justice and colleagues[27] recorded wrist activities in hospitalized schizophrenia patients. They found that changing the antipsychotic medication from haloperidol (conventional) to clozapine (atypical) improved rest/activity rhythm. They also found that patients taking atypical antipsychotic drugs showed a higher level of daytime activity than did patients taking conventional antipsychotic drugs.[28] It is conceivable that the decrease in sedating effect, which occurs when changing from conventional to atypical antipsychotic drugs, may induce more consolidated nighttime sleep and consequently improve sleep quality, as was found in our study.

Although all 4 of the atypical antipsychotic drugs used in the present study have high potency of 5-HT_2 receptor blockade, the effect of perospirone on subjective sleep quality differed from the others. The precise mechanism of this difference is not known, but it is plausible that a potent agonistic action on 5-HT_{1A} receptors by perospirone may be involved. Clozapine, the first atypical antipsychotic drug that appeared for clinical use, also has high 5-HT_{1A} receptor agonist affinity. Although clozapine improves psychotic symptoms in patients with schizophrenia,[29] its administration was reported to reduce the amount of SWS.[29–31] Similarly, the 5-HT_{1A} agonist, m-CPP, was reported to decrease SWS in healthy volunteers.[23,24] In addition, the increase in the amount of SWS correlated with the improvement of subjective sleep quality.[25,26] Taken together, these findings indicate that perospirone might deteriorate subjective sleep quality partly through a decrease of SWS by its 5-HT_{1A} receptor agonist affinity.

Our results also support early findings that the severity of psychotic symptoms may correlate with sleep quality. Kupfer and coworkers[32] reported that the waxing phase of psychosis was associated with decreased total sleep. Following antipsychotic drug treatment, clinical improvement was associated with shorter sleep latency and improvement of sleep efficiency.[33] In addition, minutes of SWS were inversely correlated with the severity of negative symptoms in never-medicated patients with schizophrenia.[5]

The correlation between subjective sleep quality and severity of psychotic symptoms was insignificant at baseline. However, changes in subjective sleep quality were significantly correlated with changes in negative symptom scores on the PANSS in the present study.

Although the results of the present study demonstrate that changing from typical to atypical antipsychotic drugs significantly improves both subjective quality of sleep and negative symptoms, the precise mechanism of this improvement is still unknown. Conventional antipsychotic drugs are generally more sedating than atypical antipsychotic drugs.[27,28] Sedated patients tend to become socially isolated. It is possible that the improvement in negative symptoms noted with administration of atypical antipsychotic drugs may be due to increased daytime alertness and activity as a result of improved sleep quality and a decreased sedative effect.

In summary, switching from conventional antipsychotic drugs to atypical antipsychotic drugs significantly improved subjective sleep quality as assessed by the PSQI. This improvement was significantly correlated with the improvement of psychotic symptoms as determined by negative scores on the PANSS. Atypical antipsychotic drugs may also be particularly beneficial for the treatment of patients with schizophrenia experiencing sleep disturbances.

When interpreting these findings, it should be considered that the limitations of this study are its lack of a crossover design, which may bias efficacy findings in favor of the atypical antipsychotic drugs, and the absence of polysomnographic measurements. Further controlled double-blind studies with a crossover design and the addition of polysomnographic measures are required to confirm these findings.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Fazaclo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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