Efficacy and safety of typical and atypical antipsychotic medications in the treatment of delirium

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Abstract

**Background** Most previous studies on the efficacy of antipsychotic medication for the treatment of delirium have reported that there is no significant difference between typical and atypical antipsychotic medications. It is known, however, that older age might be a predictor of poor response to antipsychotics in the treatment of delirium. The objective of this study was to compare the efficacy and safety of haloperidol, risperidone, olanzapine, and quetiapine for the treatment of delirium with consideration of patient age.

**Methods** This study was a 6-day, prospective clinical trial of haloperidol, risperidone, olanzapine, and quetiapine in patients with delirium at a tertiary level hospital. The subjects were referred to the consultation-liaison psychiatric service for management of delirium and were screened before enrollment in this study. A total of 80 subjects were assigned to receive either haloperidol (N=23), risperidone (N=21), olanzapine (N=18), or quetiapine (N=18). The efficacy was evaluated using the Korean version of the Delirium Rating Scale-Revised-98 (DRS-K) and the Korean version of the Mini Mental Status Examination (K-MMSE). The safety was evaluated by the Udvalg Kliniske Undersogelser side effect rating scale.

**Results** There were no significant differences in mean DRS-K severity or K-MMSE scores among the four groups at baseline. In all groups, the DRS-K severity score decreased and the K-MMSE score increased significantly over the study period. However, there were no significant differences in the improvement of DRS-K or K-MMSE scores among the four groups. Similarly, cognitive and non-cognitive subscale DRS-K scores decreased regardless of the treatment group. The treatment response rate was lower in patients over 75 years old than in patients under 75 years old. Particularly, the response rate to olanzapine was poorer in the older age group. Fifteen subjects experienced a few adverse events, but there were no significant differences in adverse event profiles among the four groups.

**Conclusions** Haloperidol, risperidone, olanzapine, and quetiapine were equally efficacious and safe in the treatment of delirium. However, age is a factor that needs to be considered when making a choice of antipsychotic medication for the treatment of delirium.

**KEY WORDS**: Delirium, Haloperidol, Risperidone, Olanzapine, Quetiapine

**Trial Registration Site**: Clinical Research Information Service, Republic of Korea, (http://cris.nih.go.kr, Registered Trial No. KCT0000632)
Background

Delirium is a common, complex neuropsychiatric disorder with a high prevalence among elderly patients, postsurgical patients, and cancer patients in advanced stages of illness [1-3]. Typically, delirium shows an abrupt, rapid onset and a fluctuating course [4]. The core features of delirium consist of disturbances in cognitive functions such as attention, memory, thought, and language [4]. However, its clinical presentation can be highly variable with a broad range of associated non-cognitive, behavioral symptoms that reflect the influence of distinct etiologies, medical comorbidities, or pharmacological treatments [5].

In hospitalized elderly patients, the prevalence of delirium ranges from 10 to 40% [6]. Delirium is associated with adverse effects such as increased mortality, functional impairment, prolonged hospitalization, and increased cost of care [7, 8]. Regardless of the evident clinical significance, delirium tends to be under-diagnosed and under-treated. Early identification and effective psychiatric treatment of delirium is important in the comprehensive care of elderly hospitalized patients[9].

The treatment of delirium includes ensuring safety with environmental or supportive interventions, identifying and treating the cause of delirium, and enhancing the patient's functioning. Regarding pharmacological intervention, antipsychotic medication has been considered the treatment of choice for delirium [10]. Haloperidol, a typical antipsychotic, has continued to be the first-line agent due to its effectiveness, relatively minor sedative and hypotensive effects and low anticholinergic side effects [10-12]. However, haloperidol may induce adverse side effects such as extrapyramidal symptoms (EPSs) or prolongation of the QTc interval and arrhythmias among patients with delirium [13-15]. EPSs are more likely to occur in elderly and seriously medically ill patients, who are also the most susceptible to delirium. In addition, it may be difficult to obtain a differential diagnosis of akathisia, one of the EPSs induced by haloperidol, based on the behavioral symptoms of delirium [16].

Recently, atypical antipsychotics such as risperidone, olanzapine, and quetiapine have been increasingly used to treat delirious patients due to the lower incidences of EPSs associated with these drugs [17]. Although a number of studies have been conducted to evaluate the efficacy or safety of atypical antipsychotics in the treatment of delirium, most of these reports have been in the form of case reports or open-label trials [18, 19]. Only two placebo-controlled, randomized trials of atypical antipsychotics for the treatment of delirium have been reported [20, 21]. Some randomized comparative trials assessing the efficacy of various antipsychotics have analyzed patients with delirium in critical care units or patients referred to consultation-liaison psychiatric services [22-27]. Three trials compared the efficacy between one atypical antipsychotic agent and haloperidol [22-24] and two trials compared the effectiveness of two different atypical antipsychotics [25, 26]. One trial assessed the comparative efficacy among two atypical antipsychotics and haloperidol [27]. Previous trials comparing the treatment response of atypical antipsychotics based on age (<70 years old, ≥70 years old) suggested that older age might predict a poor response to the treatment of delirium [26, 28]. Researchers in the field of psychiatry often divide older subjects into two groups (young-old and old-old), with an age of 74 being the cutoff point [29-31]. However, no previous research has compared the response rate to various atypical antipsychotics in the treatment of delirium based on this age grouping.

Although previous trials have reported that there was no significant difference in the efficacy between haloperidol and atypical antipsychotics in the treatment of delirium, the reported data are not sufficient to form conclusions regarding the efficacy of various atypical antipsychotics compared to haloperidol. Only a few trials have considered age as a factor
when comparing the response rates of atypical antipsychotics in the treatment of delirium. To our knowledge, no previous trial has compared the efficacy of haloperidol with more than two atypical antipsychotics in the treatment of delirium. Therefore, in this study, we compared the efficacy, safety, and response rates of haloperidol and three atypical antipsychotics (risperidone, olanzapine and quetiapine), dividing the study cohort into two age groups, for the treatment of patients with delirium.

Methods

Subject

The subjects enrolled in this study were patients presenting with a mental status change who were referred to a consultation-liaison psychiatric service at a tertiary level university hospital in Korea. To be enrolled in the study, subjects were required to meet the DSM-IV-TR diagnostic criteria for delirium [32] and to be older than 50 years. One hundred and thirteen patients who were diagnosed with delirium based on DSM-IV-TR and referred to the consultation-liaison psychiatric service were screened for this study. Twenty-two patients with delirium were excluded. The reasons for exclusion were as follows: a diagnosis of dementia or comorbid psychiatric disorder (N=8), a terminal illness (N=7), a history of prolonged QTc interval (N=3), hearing loss (N=2), neuroleptic malignant syndrome (N=1), and use of antipsychotic medication before referral (N=1). Finally, 80 patients were included in this study after excluding patients (N=11) who refused to provide informed consent.

Assessment

The definite cause of delirium for all participants was categorized using the Delirium Etiology Checklist (DEC) [33]. The DEC, which is a standardized checklist for attribution of delirium to all possible etiological causes, has 12 categories: drug intoxication, drug withdrawal, metabolic/endocrine disturbance, traumatic brain injury, seizures, intracranial infection, systemic infection, intracranial neoplasm, systemic neoplasm, cerebrovascular disease, organ insufficiency, other central nervous system disorders, or other systemic disease.

The primary efficacy was evaluated by the Korean version of the Delirium Rating Scale-Revised-98 (DRS-K) [34]. The Delirium Rating Scale-Revised-98 (DRS-R-98) is an assessment tool designed for the evaluation of symptoms of delirium consisting of 16 items [35]. The DRS-R-98 is divided into two sections consisting of a 13-item severity subscale and a 3-item diagnostic subscale. The severity scales of DRS-R-98 include two subscales: non-cognitive (items 1-8) and cognitive (items 9-13). Each item on the severity subscale is rated 0 to 3 points and each item in the diagnostic subscale is rated from 0 to 2 or 3 points. The severity subscale score ranges between 0 to 39 points, with a higher score indicating more severe delirium. A score of ≥15 is suggested to be consistent with a diagnosis of delirium. Treatment response in this study is defined as a ≥50% reduction from baseline DRS-K score.

The secondary efficacy was evaluated by the Korean version of the Mini Mental Status Examination (K-MMSE) [36]. The Mini Mental Status Examination (MMSE) is a 30 point cognitive test for the bedside assessment of cognitive function [37]. The MMSE contains 19 items and the maximum score is 30 points (10 points for orientation, 6 points for verbal memory, 5 points for concentration and calculation, 5 points for language, 3 points for praxis, 1 point for visuospatial construction).

The safety measures involved when reporting adverse events and EPSs were evaluated using the Udvalg Kliniske Undersøgelser (UKU) neurological side effect items (dystonia, rigidity, bradykinesia, tremor, and akathisia) [38].

All the subjects were evaluated at baseline and on the second, the fourth, and sixth days at
the same time of day (PM 7:00-9:00).

Procedure
This study was a 6-day, prospective clinical trial of haloperidol and three atypical antipsychotics (risperidone, olanzapine, and quetiapine) for the treatment of delirium. All subjects who fulfilled the criteria were assigned either haloperidol, risperidone, olanzapine, or quetiapine depending on the clinical and empirical judgment of the clinician. The antipsychotic medication and dose titration were decided by one of the investigators, and all assessments were carried out by another investigator who was blind to the antipsychotic drug being administered.

Dose and titration
The initial starting dose was determined on the basis of age, degree of severity of delirium, and the general medical or postsurgical condition of the individual subject. The titration of dose was adjusted according to the clinical judgment on the basis of daily clinical assessments of delirium over 6 days. A flexible dosing regimen (haloperidol: 0.5-10 mg, risperidone: 0.25-4 mg, olanzapine: 1-20 mg, quetiapine: 25-200 mg) was used. Because strict restriction of rescue medication in subjects with a poor general medical condition would have been ethically problematic, rescue intramuscular injections of haloperidol or lorazepam were allowed and recorded.

Statistical analysis
The data were analyzed using the Statistical Package for Social Scientists, version 18.0 (SPSS; Chicago, IL). Group comparisons of demographic characteristics, mean baseline DRS-K and K-MMSE scores, and the mean daily chlorpromazine equivalent dose were established using the chi-square test or Fisher’s exact test for categorized variables and one-way analysis of variance (ANOVA) for continuous variables. In this longitudinal study, because some data were missing due to dropout or other reasons such as discharge, a linear mixed model was applied [39, 40] to compare changes in DRS-K and K-MMSE scores during treatment within each group and among the four groups. Medication group, visit day, and day-by-group interaction were included as fixed effects. The group difference in treatment response and side effect profile was analyzed by the chi-square test or Fisher’s exact test. In order to examine differences in treatment response depending on age, each patient’s age was converted to a dichotomous variable with two levels (young-old: < 75 years old, old-old: ≥75 years old) [29-31]. All statistical analyses were two-tailed, with a significance level of probability set at 0.05.

Consent and approval
The study design was approved by the Institutional Review Board and the ethics committees at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Written informed consent was obtained either from the subjects’ primary caregivers or the legal representatives of the subjects prior to enrollment. Prior to screening, the objective of this study and the pharmacological treatments available were explained to them. The primary caregivers or the legal representatives of subjects had the right to withdraw consent at any time during this study. Other ethical safeguards were also maintained during the study.

Results
Demographic characteristics and causes of delirium (Table 1)
A total of 80 patients consisting of 36 men (45%) and 44 women (55%) were enrolled in this
The mean age and years of education of the subjects were 71.8 ± 11.5 years and 7.5 ± 5.6 years, respectively. There were no significant differences in sex, age and years of education between the four groups. The most common definite etiology of delirium in the study sample was metabolic-endocrine abnormality (N=23). This was followed by organ insufficiency (N=16), systemic infection (N=14), systemic neoplasm (N=12), cerebrovascular cause (N=9), and others (N=6). A comparison of the frequency of each definite etiology of delirium among the four groups revealed that the differences among the four groups were not statistically significant.

Treatment group and clinical course of delirium (Table 1)
All subjects (N=80) were assigned to receive either haloperidol (N=23), risperidone (N=21), olanzapine (N=18), or quetiapine (N=18) according to the clinical judgment of the investigator at the baseline assessment. Of the 80 subjects enrolled, 53 patients (66.2%) completed this trial. The reasons for dropout included loss to follow-up due to discharge from hospital (N=18), transfer to the intensive care unit (N=6), and withdrawal of consent (N=3). In the haloperidol group, nine of 23 patients dropped out during the study. Five subjects were discharged from the hospital, two subjects were transferred to the intensive care unit, and two subjects withdrew consent. In the risperidone group, seven of 21 subjects could not be evaluated after the fourth day because they were discharged from the hospital (N=5) or transferred to the intensive care unit (N=2). In the olanzapine group, five of 18 subjects did not complete the trial because of discharge from the hospital (N=4) or transfer to the intensive care unit (N=1). In the quetiapine group, six of 18 subjects dropped out due to discharge from the hospital (N=4), transfer to the intensive care unit (N=1), or withdrawal of consent (N=1). The difference in the dropout rate was not significant among the four groups (p=0.899). Excluding cases of dropout, the numbers of subjects who could not be evaluated at least once after the baseline assessment due to loss to follow-up or worsening medical condition were six in the haloperidol group, one in the risperidone group, two in the olanzapine group, and five in the quetiapine group.

The difference in the chlorpromazine equivalent dose between the four groups was not significant (p=0.192).

Rescue intramuscular injection of haloperidol was used 13 times in seven subjects in the haloperidol group, 12 times in nine subjects in the risperidone group, eight times in four subjects in the olanzapine group, and 15 times in nine subjects in the quetiapine group. The mean doses of rescue intramuscular haloperidol were similar among the four groups (haloperidol: 1.4±2.3 mg, risperidone: 1.4±1.8 mg, olanzapine: 1.1±2.6 mg, quetiapine: 2.3±2.6 mg, p=0.419). Rescue intramuscular lorazepam injection was used once in one subject in the haloperidol group, twice in two subjects in the risperidone group, and four times in two subjects in the olanzapine group.

The mean duration of medication among all subjects was 4.9±1.5 days. The mean duration of medication was not significantly different among the four groups (haloperidol: 4.7±1.6 days, risperidone: 5.1±1.3 days, olanzapine: 5.3±1.1 days, quetiapine: 4.8±1.7 days, p=0.655).

Efficacy analysis (Table 2)
In regards to both the primary and secondary efficacy measures of this study, the within-group effect was statistically significant in all groups. A significant serial decrease in the mean DRS-K severity score (Fig. 1) and increase in the mean K-MMSE score (Fig. 2) was observed in all groups during the study period. The day-by-group interaction effect and between-group effect was not significant in any efficacy measures.

The cognitive and non-cognitive subscale scores of the DRS-K decreased significantly over
the study period in all groups (p < 0.001). However, the rate of reduction of either subscale score did not differ significantly among the four groups during the study period (p=0.718, p=0.918).

In terms of treatment response, there was no significant difference in the response rate among the four groups (haloperidol: 15/23, 65.2%, risperidone: 14/21, 66.6%, olanzapine: 12/18, 66.6%, and quetiapine: 13/18, 72.2%, p=0.969). When response rate was compared according to demographic characteristics, no significant difference was noted according to sex (p=0.886). The response rate was significantly lower in subjects over 75 years old (15/32, 46.8%) compared to those under 75 years old (39/48, 81.2%, p=0.001) (Fig. 3). Of note, the response rate to olanzapine was much lower in subjects over 75 years old (2/7, 28.5%) compared to those under 75 years old (10/11, 90.9%, p=0.013), while the response rates of the other three groups did not differ significantly between the two age groups (p>0.05) (Fig. 3).

The difference in the mean baseline K-MMSE score among the four groups was not significant (p=0.565). In contrast to the DRS-K severity score, the mean K-MMSE score increased serially from the baseline assessment in all groups (all p < 0.001). However, the rate of improvement in the K-MMSE score did not differ significantly among the four groups (p=0.630).

### Safety analysis (Table 3)

Overall, all subjects tolerated the four antipsychotics well. Fifteen (18.8%) of the total subjects experienced some adverse events. Exacerbation of sedation or sleepiness was reported in four subjects in both the haloperidol and olanzapine groups, three subjects in the risperidone group, and two subjects in the quetiapine group. Rigidity was reported in two subjects in the haloperidol group, and one subject in each of the other three groups. Bradykinesia was reported in one subject in each of the haloperidol, risperidone, and olanzapine groups. Tremors were reported in three subjects in the haloperidol group, two subjects in the risperidone group, and one subject in each of the olanzapine and quetiapine groups. Akathisia was only reported in one subject in the haloperidol group. All extrapyramidal side effects were tolerable and mild in severity. When the number of subjects experiencing side effects was compared among the four groups, the difference was not statistically significant.

### Discussion

Recently, a number of researchers have reported that atypical antipsychotics may be as effective as haloperidol in treating delirium. Risperidone, olanzapine, and quetiapine have been increasingly used for pharmacologic intervention of delirium. Previous research has shown that the efficacy of risperidone and olanzapine is not different from that of haloperidol in the treatment of delirium [22-24, 27, 41, 42]. Quetiapine has been reported to be as efficacious as haloperidol [43, 44] and to reduce the severity of the symptoms of delirium more rapidly than placebo [20]. To date, most randomized comparative trials of atypical antipsychotics in the treatment of delirium have compared the efficacy of one atypical antipsychotic agent and haloperidol [22-24] or two different antipsychotics [25, 26]. Only one randomized comparative study has compared the efficacy of two different atypical antipsychotics and haloperidol [27]. To our knowledge, this study is the first trial to compare the efficacy and safety among haloperidol and three atypical antipsychotics. In the present study, haloperidol, risperidone, olanzapine and quetiapine were equally effective in improving the symptoms of delirium. There was no significant difference in the rate of
reduction of DRS-K severity score and improvement of K-MMSE score with time among the four groups. Recently, one comparative efficacy study of haloperidol, risperidone, and olanzapine showed that risperidone and olanzapine were as efficacious as haloperidol in treating delirium [27]. Our result supports the findings of previous research with regard to the comparative efficacy of the three atypical antipsychotics versus haloperidol in managing symptoms of delirium [22-24, 27, 41-44]. The mean daily doses of risperidone, olanzapine, and quetiapine were not largely different from those of previous studies [14, 23, 24, 26, 27, 44-46]. This finding also suggests that a relatively low dose of atypical antipsychotics may be effective in managing the symptoms of delirium [23, 24, 27, 44-46].

In terms of the rate of reduction of the cognitive and non-cognitive subscale scores of the DRS-K, the group difference was not significant over the study period. There have been no previous studies to have assessed the difference in the efficacy of atypical antipsychotics in terms of the cognitive and non-cognitive subscale score of the DRS-R-98, with the exception of one placebo, controlled trial [20]. Even though further study regarding the differences in the efficacy of antipsychotics in the two different symptom domains of delirium is needed, the results of our study suggest that haloperidol, risperidone, olanzapine, and quetiapine may be equally effective in the treatment of both the cognitive and non-cognitive symptoms of delirium.

The demographic characteristics of the subjects enrolled in this study were not significantly different from those of subjects in previous studies [23, 25, 27]. In regards to the causes of delirium, the most common definite cause of delirium was metabolic or endocrine disturbance, a finding which was similar to that of a previous study of patients with delirium referred to a consultation-liaison psychiatric service [27].

In the present study, the response rate to olanzapine was poor in subjects over 75 years old compared to those under 75 years old. However, the response rate to the other three antipsychotics was not significantly different between age groups. A previous study reported that old age was associated with poorer response to olanzapine in hospitalized cancer patients with delirium [28], while another study reported that the response rate of olanzapine was similar depending on age, but that the response rate to risperidone was much lower in an older age group [26]. The major neurotransmitter hypothesized to be involved in delirium is acetylcholine, and several studies have reported that a variety of delirium-inducing factors are associated with decreased acetylcholine activity in the brain [47]. In regards to the pharmacological profile, olanzapine is known to have a significant affinity for muscarinic receptors and to induce relatively more anticholinergic adverse effects than the other three antipsychotics [48, 49]. Age-related differences in susceptibility to anticholinergic adverse effects might have affected the response rate in the olanzapine group. In addition, this might be related to differences in the general underlying medical condition, as the frequency of organ insufficiency was relatively higher in the olanzapine group than in the other three groups. These results suggest that advanced age is not only a risk factor for delirium, but also may be a predictor of poor response to delirium treatment. Further investigation of the impact of age on treatment response is required.

There were no significant group differences in the number of subjects experiencing adverse events or in the type of adverse events. Although previous review articles have suggested that atypical antipsychotics are safe, with a lower rate of adverse events compared to haloperidol in the treatment of delirium [10, 13], a Cochrane review reported that haloperidol at a low dosage (<3.5 mg/day) was safe, with a similar frequency of adverse events compared to atypical antipsychotics [41]. In this study, the mean daily dose of haloperidol was relatively low (1.2 ± 0.4 mg/day) and the total duration of medication was relatively short. Thus, the results of the present study suggest that a low dose of haloperidol is safe and does not show a
greater frequency of EPSs compared to atypical antipsychotics over a relatively short period of treatment.

This study has several limitations. First, the small sample size of our study might compromise the generalizability of the results. Second, although the rater was blind to which study drug was being administered, as the rater knew that all subjects were receiving active treatment, the ratings could have been affected. Third, confounding factors associated with rescue medication could not be rigidly controlled due to ethical considerations. The permission to use rescue medication might not have seriously affected the results of this study because the total mean dose of intramuscular rescue injection of haloperidol was not significantly different among the four groups. If the dosing titration of the study drugs had been escalated more rapidly, the need for rescue medication could have been decreased. Fourth, the dropout rate was relatively high, and the missing data caused by dropouts could affect the result of this study. In order to overcome this limitation, we used a linear mixed model, in which all available data can be included and missing data can be appropriately addressed [39, 40]. By using the average area under each subject’s rating scale trajectory, we could compare treatment groups across whole study period. In addition, changes in the various medical or surgical conditions of the study subjects might have affected the symptom severity of delirium, regardless of the use of antipsychotics. Finally, as the symptoms of delirium can fluctuate and improve irrespective of the treatment given, the findings of our study must be understood in the background of these limitations. Regardless of these limitations, the results of the present study could provide important clinical information regarding the usefulness of commonly prescribed antipsychotics in the treatment of delirium with various underlying etiologies in a tertiary hospital setting.

Conclusions
In conclusion, the atypical antipsychotics risperidone, olanzapine, and quetiapine and low dose haloperidol were equally effective and safe in the treatment of delirium. The treatment response rate was significantly lower in subjects over 75 years old than in subjects under 75 years old, particularly in the olanzapine group. The factor of age needs to be considered in the choice of antipsychotic medication for the treatment of delirium. Further prospective randomized clinical trials of a larger patient group with delirium should be carried out to confirm and replicate our findings.

List of Abbreviations used
EPSs: extrapyramidal symptoms
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision
DEC: Delirium Etiology Checklist
DRS-K: Korean version of the Delirium Rating Scale-Revised-98
DRS-R-98: Delirium Rating Scale-Revised-98
K-MMSE: Korean version of the Mini Mental Status Examination
MMSE: Mini Mental Status Examination
UKU: Udvalg Kliniske Undersogelser
SPSS: Statistical Package for Social Scientists
ANOVA: one-way analysis of variance

Competing interests
The authors declare that they have no competing interests.
Authors' contributions

All authors participated in the design of the trial and read and approved the final manuscript.

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Figure 1. Serial changes in DRS-K severity scores in the four antipsychotic groups
Mean changes in DRS-K severity scores with 95% confidence intervals.
In all antipsychotic groups, the mean DRS-K score severity decreased significantly over the study period (all p-values analyzed by linear mixed model statistics < 0.0001). However, there were no significant differences in the degree of reduction in mean DRS-K severity score with time among the four groups (p-values analyzed by linear mixed model statistics = 0.779).

Figure 2. Serial changes in K-MMSE scores in the four antipsychotic groups
Mean changes in K-MMSE scores with 95% confidence intervals.
In all antipsychotic groups, the mean K-MMSE score increased significantly over the study period (all p-values analyzed by linear mixed model statistics < 0.0001). However, there was no significant difference in the degree of improvement in mean K-MMSE score with time among the four groups (p-values analyzed by linear mixed model statistics = 0.630).

Figure 3. Treatment response rate between young-old and old-old groups in the four antipsychotic groups
* p < 0.05 by Chi-square test or Fisher’s exact test
Treatment response was defined as a ≥50% reduction from the baseline DRS-K score.

Table 1. Group comparisons of demographic characteristics, causes of delirium, medication, and number of subjects assessed.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Haloperidol N=23</th>
<th>Risperidone N=21</th>
<th>Olanzapine N=18</th>
<th>Quetiapine N=18</th>
<th>Total N=80</th>
<th>Sig.</th>
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<tbody>
<tr>
<td>Age, mean±SD, year</td>
<td>74.0±9.9</td>
<td>70.1±9.5</td>
<td>69.5±15.9</td>
<td>73.3±10.7</td>
<td>71.8±11.5</td>
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<td>Education, mean±SD, year</td>
<td>5.8±4.5</td>
<td>8.7±6.9</td>
<td>8.5±6.4</td>
<td>7.3±3.9</td>
<td>7.5±5.6</td>
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<td>Gender, male, N(%)</td>
<td>12(52.2)</td>
<td>8(38.1)</td>
<td>8(44.4)</td>
<td>8(44.4)</td>
<td>36(45)</td>
<td>0.828</td>
</tr>
<tr>
<td>Cause of delirium, N(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metabolic/endocrine</td>
<td>6(26.0)</td>
<td>8(38.0)</td>
<td>4(22.2)</td>
<td>5(27.7)</td>
<td>23(28.7)</td>
<td>0.759</td>
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<td>Systemic infection</td>
<td>4(17.3)</td>
<td>3(14.2)</td>
<td>3(16.6)</td>
<td>4(22.2)</td>
<td>14(17.5)</td>
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<td>Systemic neoplasm</td>
<td>6(26.0)</td>
<td>1(4.7)</td>
<td>3(16.6)</td>
<td>2(11.1)</td>
<td>12(15.0)</td>
<td>0.260</td>
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<td>Cerebrovascular</td>
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<td>3(14.2)</td>
<td>0(0.0)</td>
<td>3(16.6)</td>
<td>9(11.2)</td>
<td>0.328</td>
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<td>Organ insufficiency</td>
<td>3(13.0)</td>
<td>3(14.2)</td>
<td>8(44.4)</td>
<td>2(11.1)</td>
<td>16(20.0)</td>
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<td>Others</td>
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<td>3(14.2)</td>
<td>0(0.0)</td>
<td>2(11.1)</td>
<td>6(7.5)</td>
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<td>Dose, mean±SD, mg/day</td>
<td>1.2±0.4</td>
<td>1.1±0.3</td>
<td>2.9±1.0</td>
<td>47.9±17.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalent dose, mean±SD, mg/day</td>
<td>60.0±21.4</td>
<td>56.3±16.8</td>
<td>59.8±20.5</td>
<td>63.9±22.8</td>
<td>59.8±20.4</td>
<td>0.192</td>
</tr>
<tr>
<td>Duration of medication, mean±SD, day</td>
<td>4.7±1.6</td>
<td>5.1±1.3</td>
<td>5.3±1.1</td>
<td>4.8±1.7</td>
<td>4.9±1.5</td>
<td>0.655</td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23(100.0)</td>
<td>21(100.0)</td>
<td>18(100.0)</td>
<td>18(100.0)</td>
<td>80(100.0)</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>18(78.2)</td>
<td>21(100.0)</td>
<td>18(100.0)</td>
<td>15(83.3)</td>
<td>72(90.0)</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>16(69.5)</td>
<td>18(85.7)</td>
<td>15(83.3)</td>
<td>12(66.6)</td>
<td>61(76.2)</td>
<td></td>
</tr>
<tr>
<td>N(%)</td>
<td>14(60.8)</td>
<td>14(66.6)</td>
<td>13(72.2)</td>
<td>12(66.6)</td>
<td>53(66.2)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Group comparisons of serial changes in DRS-K and K-MMSE scores.

†: p-values analyzed by linear mixed model statistics.

<table>
<thead>
<tr>
<th>Efficacy measures</th>
<th>Haloperidol mean±S.D.</th>
<th>Risperidone mean±S.D.</th>
<th>Olanzapine mean±S.D.</th>
<th>Quetiapine mean±S.D.</th>
<th>Total mean±S.D.</th>
<th>Sig. among groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRS-K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severity Baseline</td>
<td>17.4±6.7</td>
<td>18.9±5.2</td>
<td>17.5±5.7</td>
<td>17.5±6.4</td>
<td>17.8±6.0</td>
<td>0.779*</td>
</tr>
<tr>
<td>score Day 2</td>
<td>11.5±7.1</td>
<td>13.3±5.8</td>
<td>10.5±6.6</td>
<td>12.2±5.4</td>
<td>11.93±6.2</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>8.5±4.6</td>
<td>9.8±6.7</td>
<td>8.8±6.0</td>
<td>7.6±3.7</td>
<td>8.80±5.4</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>7.7±5.4</td>
<td>8.3±7.1</td>
<td>8.1±5.5</td>
<td>6.5±4.0</td>
<td>7.75±5.5</td>
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</tr>
<tr>
<td>cognitive Baseline</td>
<td>7.8±3.8</td>
<td>8.7±3.4</td>
<td>7.7±3.6</td>
<td>8.1±3.2</td>
<td>8.14±3.5</td>
<td>0.718*</td>
</tr>
<tr>
<td>subscale Day 2</td>
<td>5.7±3.9</td>
<td>6.5±3.4</td>
<td>5.0±3.0</td>
<td>5.6±2.6</td>
<td>5.76±3.3</td>
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</tr>
<tr>
<td>score Day 4</td>
<td>4.3±2.4</td>
<td>4.8±3.6</td>
<td>4.2±3.2</td>
<td>4.0±2.5</td>
<td>4.43±3.0</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>4.0±2.9</td>
<td>4.1±4.0</td>
<td>4.2±2.7</td>
<td>3.2±2.5</td>
<td>3.94±3.1</td>
<td></td>
</tr>
<tr>
<td>non-cognitive Baseline</td>
<td>9.5±3.5</td>
<td>10.1±3.0</td>
<td>9.7±3.3</td>
<td>9.4±4.2</td>
<td>9.73±3.4</td>
<td>0.918*</td>
</tr>
<tr>
<td>cognitive Day 2</td>
<td>5.7±3.5</td>
<td>6.5±2.9</td>
<td>5.5±3.8</td>
<td>6.6±3.7</td>
<td>6.11±3.4</td>
<td></td>
</tr>
<tr>
<td>subscale Day 4</td>
<td>4.1±2.6</td>
<td>4.9±3.8</td>
<td>4.6±3.5</td>
<td>3.6±2.2</td>
<td>4.41±3.1</td>
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<tr>
<td>score Day 6</td>
<td>3.7±2.8</td>
<td>4.2±3.6</td>
<td>3.9±3.5</td>
<td>3.3±2.0</td>
<td>3.81±3.0</td>
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</tr>
<tr>
<td>K-MMSE score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.7±6.5</td>
<td>15.0±5.8</td>
<td>16.2±5.4</td>
<td>15.7±6.3</td>
<td>15.1±6.0</td>
<td>0.630*</td>
</tr>
<tr>
<td>Day 2</td>
<td>19.0±6.7</td>
<td>18.3±5.7</td>
<td>21.0±6.2</td>
<td>20.2±4.9</td>
<td>19.5±5.9</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>21.3±5.7</td>
<td>21.5±5.3</td>
<td>21.8±5.8</td>
<td>21.9±3.7</td>
<td>21.6±4.9</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td>22.4±4.4</td>
<td>22.4±5.0</td>
<td>23.1±5.3</td>
<td>23.4±3.7</td>
<td>22.8±4.6</td>
<td></td>
</tr>
</tbody>
</table>

Each day-by-group interaction was not significant in all efficacy measures.
(all p-values analyzed by linear mixed model statistics > 0.05)

In all medication groups, the mean score of DRS-K severity, cognitive and non-cognitive subscale tended to decrease significantly over study period.
(all p-values analyzed by linear mixed model statistics < 0.0001)

In all medication groups, the mean score of K-MMSE tended to increase significantly over the study period. (all p-values analyzed by linear mixed model statistics < 0.0001).

Table 3. Group comparisons of frequency of UKU side effect rating scale items.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Haloperidol N(%)</th>
<th>Risperidone N(%)</th>
<th>Olanzapine N(%)</th>
<th>Quetiapine N(%)</th>
<th>Total (N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation/Sleepiness</td>
<td>4(17.3)</td>
<td>3(14.2)</td>
<td>4(22.2)</td>
<td>2(11.1)</td>
<td>13(16.2)</td>
<td>0.838</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Rigidity</td>
<td>2(8.7)</td>
<td>1(4.7)</td>
<td>1(5.5)</td>
<td>1(5.5)</td>
<td>5(6.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>1(4.3)</td>
<td>1(4.7)</td>
<td>1(5.5)</td>
<td>0(0)</td>
<td>3(3.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Tremor</td>
<td>3(13.0)</td>
<td>2(9.5)</td>
<td>1(5.5)</td>
<td>1(5.5)</td>
<td>7(8.7)</td>
<td>0.869</td>
</tr>
<tr>
<td>Akathisia</td>
<td>1(4.3)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>1(1.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total number of subjects who had side effects</td>
<td>5(21.7)</td>
<td>4(19.0)</td>
<td>4(22.2)</td>
<td>2(11.1)</td>
<td>15(18.7)</td>
<td>0.857</td>
</tr>
</tbody>
</table>