A Randomized Controlled Trial of Risperidone and Olanzapine for Schizophrenic Patients With Neuroleptic-Induced Tardive Dyskinesia

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Objective: To compare the efficacy of risperidone and olanzapine in schizophrenic patients with tardive dyskinesia on treatment with first-generation antipsychotics.

Method: We conducted a 24-week, rater-blinded, flexible-dose study. Sixty patients with *DSM-IV* schizophrenia (n = 58) or schizoaffective disorder (n = 2) met the *DSM-IV* research criteria for neuroleptic-induced tardive dyskinesia and were randomly assigned to a risperidone or olanzapine group. The primary outcome was a comparison of the change in the total scores on the Abnormal Involuntary Movement Scale (AIMS) from baseline to study end point between the groups. The study was conducted from July 2000 to June 2004.

Results: The mean ± SD doses of risperidone and olanzapine from baseline to study end point were 1.9 ± 0.7 to 4.1 ± 1.4 mg/d and 8.1 ± 2.0 to 12.6 ± 5.4 mg/d, respectively. There were no statistically significant differences in demographic data, severity of tardive dyskinesia, or psychotic symptoms between risperidone and olanzapine groups at baseline assessment. Both groups showed significant improvement in mean ± SD AIMS total scores (risperidone: −7.4 ± 6.9, $P < .0001$; olanzapine: −6.2 ± 8.0, $P = .0002$). However, there was a more statistically significant change in the slope of AIMS total scores in the risperidone group than in the olanzapine group ($P = .0001$).

Conclusions: Our findings demonstrated that olanzapine may not have better potential for tardive dyskinesia improvement than risperidone did. Double-blinded, fixed dose studies with a larger sample size on schizophrenic patients with tardive dyskinesia from different ethnic groups are needed to confirm the results of our study.

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Many patients with schizophrenia experience tardive dyskinesia after the long-term treatment of first-generation antipsychotics (FGAs). The tardive dyskinesia incidence rate may be as high as 5% per year, and, in previous studies, the prevalence was about 20%.[1,2] The risk factors for neuroleptic-induced tardive dyskinesia include old age, female gender, histories of neuroleptic-induced extrapyramidal syndrome (EPS), diabetes, mood disorder, and doses and duration of total neuroleptic exposure.[3] Tardive dyskinesia might be irreversible and could cause personal embarrassment and emotional distress, and tardive dyskinesia could impact one's physical, social, and occupational functions.[4] Tardive dyskinesia may also decrease adherence to antipsychotics among schizophrenia patients, thus leading to relapse and rehospitalization.[5,6]

Some studies[7,8] showed that second-generation antipsychotics (SGAs) might have a lower liability for EPS, better drug adherence, and a lower relapse rate than FGAs. Therefore, SGAs are considered a good choice for patients who had FGA-induced tardive dyskinesia. SGAs have some advantages in treating schizophrenic patients, but many countries cannot use them as first-line medications due to higher cost.[9] The National Health Insurance Bureau of Taiwan had restrictive regulations for the use of SGAs before 2003. In recent years, although the government has loosened regulations on the use of SGAs, many psychiatrists in Taiwan still need to prescribe FGAs as the first-line medications due to the limitations of global budget policy for hospitals.[10]

Different SGAs have different pharmacologic mechanisms and were classified as serotonin-dopamine antagonists, multiacting receptor targeted agents, selective D_2 and D_3 dopamine receptor antagonist, and dopamine receptor partial agonist[11]; however, little is known about which class of SGA is superior over the other classes of SGAs for those schizophrenic patients with tardive dyskinesia**.** Although several studies have demonstrated the effectiveness of clozapine in improving tardive dyskinesia, many severe clozapine-induced adverse effects have prevented it from being a suitable first-line antipsychotic.[12,13] There were few randomized controlled studies of other SGAs focusing on the treatment of patients with neuroleptic-induced tardive dyskinesia. Chouinard[14] analyzed the results of a multicenter study on fixed-dose risperidone in Canada and found that 6 mg/d of risperidone was more effective than haloperidol and placebo in treating tardive dyskinesia. A double-blind, placebo-controlled study[15] of risperidone showed that the group receiving risperidone 6 mg/d compared to a placebo group had a significant improvement in total Abnormal Involuntary Movement Scale (AIMS) scores. A single-blind comparison study on the usages of quetiapine and haloperidol in schizophrenia patients with tardive dyskinesia showed that quetiapine 400 mg/d could more significantly

improve tardive dyskinesia than haloperidol 8.5 mg/d.[16] A single-arm, blinded, randomized dose-reduction study demonstrated that olanzapine improved preexisting tardive dyskinesia during 8-month treatment.[17] However, there were limitations to this study. First, there was no control group. Second, like other observational studies on the effectiveness of olanzapine in treating tardive dyskinesia, the results may be influenced by selection or measurement bias.[18,19] There are only observational studies or case reports on tardive dyskinesia patients treated with other SGAs.[20–26] To our knowledge, there has been no published head-to-head studies comparing different SGAs in patients with tardive dyskinesia.

Risperidone and olanzapine might have different EPS severity, efficacy on psychotic symptoms, and other domains due to different receptor profiles.[27] Positron emission tomography studies showed risperidone had tighter dopamine D_2 receptor binding than olanzapine.[28,29] Furthermore, olanzapine can selectively act on dopamine mesolimbic pathway and is less likely to act on nigrostriatal pathway.[30] Besides, risperidone and olanzapine had different strength in 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α-adrenergic, histamine, and muscarinic receptors binding.[31] Hence, it is expected that risperidone and olanzapine might have different effectiveness in schizophrenia with tardive dyskinesia populations. Our hypothesis is that olanzapine is more likely than risperidone to improve tardive dyskinesia in schizophrenic patients because of less dopamine D_2 receptors blockade and less EPS potential of olanzapine than risperidone.[29] We thus initiated a randomized, head-to-head, controlled study to compare the efficacy of risperidone and olanzapine in Han-Chinese schizophrenic patients with FGAs-induced tardive dyskinesia.

METHOD

The study protocol was approved by the Research Ethics Committee of a public mental hospital in North Taiwan before implementation. We conducted the study at this public mental hospital from July 2000 to June 2004 in accordance with the principles of the Helsinki Declaration and Good Clinical Practice. All patients or legal guardians gave their written informed consent after the study purpose and procedures had been fully explained to them, before their participation in the study.

Inclusion and Exclusion Criteria

Inclusion criteria included patients who were aged 18–70 years; were female and did not have plans to become pregnant and who agreed to use reliable contraception methods if at childbearing age; met the *DSM-IV* criteria for schizophrenia, schizophreniform or schizoaffective disorder; fulfilled *DSM-IV* neuroleptic-induced tardive dyskinesia research criteria, with a severity of tardive dyskinesia no less than moderate degree (≥ 4) as assessed by the global impression of Extrapyramidal Syndrome Rating Scale (ESRS) (item 42 of the ESRS)[32]; and agreed or had legal guardians who agreed to join the study and signed an informed consent. Exclusion criteria included patients with other Axis I diagnoses in the *DSM-IV*; major systemic diseases in unstable condition; a history of neurologic disorders that would influence the tardive dyskinesia assessment; and substance abuse or dependence other than coffee or tobacco in the last 6 months before the study. All eligible patients received a psychiatric evaluation to decide whether they met the inclusion or exclusion criteria at the screening visit.

Clinical Assessments

The Brief Psychiatric Rating Scale (BPRS [18 items: score, 1–7; range, 7–126]),[33] and the Clinical Global Impression-Severity (CGI-S [range, 1–7])[34] were used to assess the severity of psychotic symptoms, the global impression of the ESRS (4 items: dyskinesia, parkinsonism, dystonia, and akathisia; score, 0–8 for each item) for EPS, and the AIMS (10 items: score, 0–4; range, 0–40) for tardive dyskinesia.[35] ESRS global impression can conveniently assess global impression in other EPS, such as parkinsonism, dystonia, and akathisia, and supplementary to AIMS rating. Two investigators (C.-H.C. and J.-J.C.) served as blinded raters. They received video training for using the AIMS and ESRS and performed interrater reliability through joint assessment of 10 patients with tardive dyskinesia and EPS before the study. The criterion of agreement is within ± 1 point of expert ratings as the manual for the ESRS.[32] The coefficients of agreement for the AIMS and global impression of ESRS were 0.91 and 0.75 among the 10 patients, respectively.

The primary outcome of this study was to compare the mean changes in the AIMS total scores from baseline to study end point between the risperidone and olanzapine groups. Secondary outcomes were to compare the differences in the changes of the ESRS, BPRS, and CGI-S scores between these 2 groups. On the basis of previous studies' results, a 50% or more decrease in AIMS total scores from baseline to study end point was set a priori as treatment responder.[13,16]

Study Design

Eligible patients fulfilling inclusion and exclusion criteria entered a washout period of 3 to 7 days prior to randomization. The patients stopped using any antipsychotics, mood stabilizers, antidepressants, and dopamine agonists during the washout period and throughout the entire study period. Screening would take place after 1 injection cycle had passed since the last injection if the patients had received depot medications prior to the study. Anticholinergic drugs, propranolol and daytime benzodiazepines were allowed during the washout period but were discontinued when the study period started. If patients had acute dystonia, parkinsonism, or akathisia at later study period, anticholinergic drugs, propranolol and daytime benzodiazepines could be prescribed under clinical decision. Patients having at least moderate degree of tardive dyskinesia at baseline visit (item 42 of ESRS ≥ 4) were then randomly assigned to receive either olanzapine or risperidone with a 1-to-1 ratio by coin method with a 6-block design. The study period lasted

24 weeks. The BPRS, CGI-S, AIMS and global impression of ESRS were performed at baseline and at weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 or at end point visit by blinded-rater. Information on adverse events, body weight, vital signs, concomitant medications, and the dosage of study medications were recorded by the attending physicians. No more than 8 mg/d of intramuscular lorazepam was given to the patients who had agitated or exhibited violent behavior.

Dosing Strategy

This study was a flexible-dose design; the dose ranges for risperidone and olanzapine were 0.5–6.0 mg/d and 2.5–20.0 mg/d, respectively. The dose range was determined based on the suggested optimal dose for general schizophrenic patients in Taiwan (risperidone 2–6 mg/d, olanzapine 10–20 mg/d).[36] Once patients appear to have tardive dyskinesia, American Psychiatric Association schizophrenia treatment guideline suggest tapering dose of FGAs to alleviate its severity.[37] Hence, we hypothesized that patients with tardive dyskinesia may need lower doses and decided to use a dose range that was one-quarter lower than the dose range for general schizophrenic patients as the lower dose range of our study. The doses were adjusted according to the clinical decisions of the nonblinded investigators. Drug compliance was assessed by counting the medications left. Study protocol was violated if a patient's medication uptake was below 80% or above 120%, and the patient was required to withdraw from the study early.

Statistical Methods

All patients who were randomly assigned and had at least 1 postbaseline assessment were included in the intent-to-treat (ITT) analysis. If the ITT subjects withdrew from the study earlier than scheduled, then the last observation carried forward method was employed to extend the end point scores. For between-group analysis, χ^2 or Fisher exact test and independent *t* test were performed for categorical and continuous data, respectively. The linear mixed model was used for continuous variables that were repeatedly measured. All results were expressed as means and standard deviations. The level of significant difference was 1-sided, $P < .05$ for the AIMS total scores change comparison due to superiority hypothesis testing. The other statistics were 2-sided, $P < .05$. The data were analyzed using the Chinese version of SAS 9.1 (SAS Institute Inc, Cary, North Carolina).

Sample Size Calculation

Our hypothesis is that olanzapine is more effective in tardive dyskinesia improvement than risperidone, due to lower dopamine D_2 receptors affinity and less hypersensitivity mechanism appeared. The sample size was calculated based on 2 previous risperidone studies,[15,38] which showed that risperidone decreased on AIMS total scores in tardive dyskinesia patients by 5 in the ITT population, and we had a case report[39] which showed that after 6 months of olanzapine treatment, AIMS total scores decreased by 12 in a tardive dyskinesia patient. We hypothesized that subjects who terminate early from this study would be followed up for 3 months on average, about half of the study period, and that one-third of subjects in the olanzapine group would drop out, resulting in AIMS total scores decreasing by 6, only half as much as those in patients who completed the study. Then the AIMS total scores in the ITT population of olanzapine group decreased by 10 on average after the combination of one-third dropouts and two-thirds patients who completed the study ($[1/3 \times 6] + [2/3 \times 12] = 10$). Under the conditions of $\alpha = .05$ 1-sided, 80% power, and a standard deviation of 7.5, we needed at least a total of 58 ITT subjects.

RESULTS

Patient Disposition and Demographics

Eighty-one patients were screened and entered a 3- to 7-day washout period. Twenty-one patients were excluded before randomization with the following reasons: misclassification as tardive dyskinesia (n = 8), less than moderate tardive dyskinesia severity after 7-day washout period (n = 5), other criteria not met (n = 4), patient withdrew consent (n = 2), and worsening of psychotic symptoms (n = 2). The remaining 60 patients were allocated by randomization, with 30 patients in each group. All 60 patients received study medications and had at least 1 postbaseline assessment. Nine and 7 patients left the study early in the risperidone and olanzapine groups, respectively. The participant flowchart and the reasons for early termination are shown in Figure 1.

There were 58 patients with schizophrenia and 2 patients with schizoaffective disorder. The study population comprised chronic schizophrenic patients whose mean age was about 40 years and exhibited moderate to severe psychotic symptoms. The mean duration of neuroleptic exposure was about 10 years. After the washout period, AIMS total scores from screening visit to baseline visit was 14.9 ± 2.2 to 17.2 ± 4.6 in the risperidone group and from 17.7 ± 6.0 to 19.4 ± 6.1 in the olanzapine group. All of the subjects received FGAs prior to participation in this study. The FGAs (the risperidone group, the olanzapine group) used prior to the study were as follows: sulpiride (n = 10, n = 11), haloperidol (n = 5, n = 7), zotepine (n = 3, n = 4), chlorpromazine (n = 3, n = 2), thioridazine (n = 3, n = 1), flupenthixol (n = 2, n = 2), pipotiazine (n = 2, n = 0), clopenthixol (n = 1, n = 3) and loxapine (n = 1, n = 0). There were no significant differences between the 2 treatment groups in the distribution of prior FGAs (χ^2 or Fisher exact *P* values ranging from 0.492 to 1). Table 1 illustrates the baseline characteristics of the study population. There were no statistically significant between-group differences in age, sex, duration of illness of schizophrenia, duration of antipsychotic treatment, duration of tardive dyskinesia, AIMS total scores, global impression of dyskinesia, parkinsonism, dystonia, and akathisia on ESRS, BPRS total scores, CGI-S, and body weight at the baseline visit. There were no between-group differences in prescreening chlorpromazine equivalent dose and the lengths of washout period.

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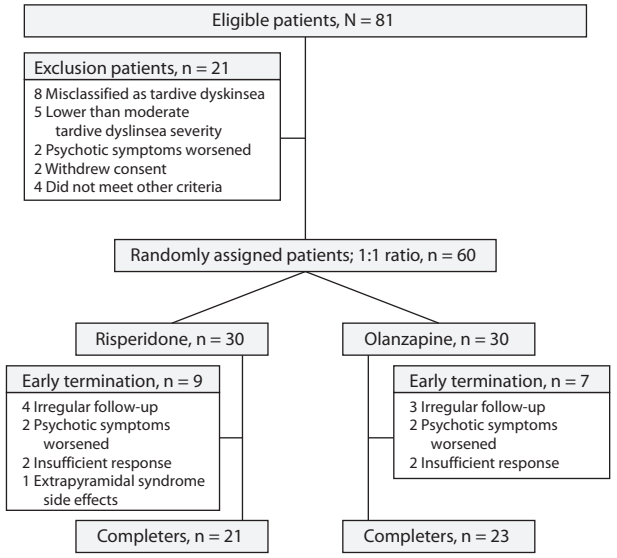
Figure 1. Summary of Participant Flowchart



Dose of Study Medications

The dosages used in the risperidone and the olanzapine groups were gradually increased from baseline to end point. For the risperidone group, the mean doses were 1.9 ± 0.7 (baseline), 2.5 ± 1.3 (first week), 3.1 ± 1.3 (second week), 3.4 ± 1.5 (third week), 3.8 ± 1.6 (fourth week), 4.2 ± 1.4 (eighth week), 4.2 ± 1.4 (12th week), 4.3 ± 1.4 (16th week), 4.1 ± 1.5 (20th week), and 4.1 ± 1.4 (24th week) mg/d. For the olanzapine group, the mean doses were 8.1 ± 2.0 (baseline), 10.0 ± 3.9 (first week), 11.9 ± 4.5 (second week), 12.9 ± 5.2 (third week), 12.5 ± 5.3 (fourth week), 13.1 ± 4.3 (eighth week), 13.1 ± 4.4 (12th week), 12.4 ± 5.2 (16th week), 12.6 ± 4.7 (20th week) and 12.6 ± 5.4 (24th week) mg/d.

Concomitant Medications

The overall use of concomitant anticholinergic drugs during the study was significantly higher in the risperidone group than in the olanzapine group (n/n = 8/30 vs n/n = 2/30; OR = 5.1; 95% CI, 1.0–26.4; $P = .04$). Although there was a higher percentage of concomitant propranolol usage to treat akathisia in the risperidone group during the study, the between-group difference was not statistically significant (n/n = 3/30 vs n/n = 1/30, $P = .6$). The incidences of concomitant daytime benzodiazepines to treat akathisia in these 2 groups were the same (n/n = 2/30 vs n/n = 2/30). One case in the risperidone group and 2 cases in the olanzapine group needed to use intramuscular lorazepam to manage agitated symptoms.

EPS and Psychotic Symptoms Assessments

Paired *t* test revealed significant reduction in AIMS total scores (risperidone, $P < .0001$; olanzapine, $P = .0002$) and global impression of ESRS dyskinesia (risperidone, $P = .002$; olanzapine, $P < .001$) from baseline to study end point in both groups; yet, significant reduction in the global impression of parkinsonism ($P = .01$) and akathisia ($P < .05$) was noted only in the olanzapine group. There was significant reduction in CGI-S in the risperidone group only ($P = .02$). There were no significant reduction in both groups in terms of the BPRS total scores and global impression of dystonia.

Independent *t* test showed that there was no significant difference in AIMS total score changes from baseline to study end points between the 2 treatment groups. The proportions of patients meeting response criteria were also not significantly different (OR = 1.75; 95% CI, 0.62–4.97; $P = .29$) between risperidone (14/30, 47.7%) and olanzapine (n/n = 10/30, 33.3%). Except global impression of parkinsonism and dystonia of ESRS, the changes in all other rating scale assessments (global impression of dyskinesia and akathisia of ESRS, CGI-S, and BPRS) showed no significant differences between groups (Table 2).

Figure 2 illustrates the AIMS total scores of each visit. An unstructured, covariance-matrix mixed model was used for repeated measurements, which tested the changes in the slopes of AIMS total scores and global impression of ESRS dyskinesia. The risperidone group showed more significant improvement in AIMS total scores ($F_{1,538} = 14.74$, $P = .0001$) and global impression of ESRS dyskinesia ($F_{1,538} = 13.47$, $P = .0003$) than the olanzapine group. However, the olanzapine group showed more statistically significant decrease than the risperidone groups in global impression of parkinsonism of ESRS ($F_{1,538} = 6.4$, $P = .01$). There were no significant slope differences between groups in the other assessments.

Safety Results

Table 3 describes adverse events among patients. There were no significant between-group differences in adverse events. The common adverse events (≥10%) in the risperidone group were headache, nausea, dizziness, drowsiness, weakness, palpitation, and constipation. As for the olanzapine group, the common adverse events included headache, dizziness, thirst, drowsiness, weakness, and muscle ache. For those who completed the entire study, the mean ± SD gains in body weight were 4.9 ± 7.1 kg and 4.6 ± 6.0 kg for risperidone and olanzapine groups, respectively. There were 42.9% (9/21) and 47.8% (11/23) of patients in risperidone and olanzapine groups that had greater than 7% of body weight gain, respectively. The differences seen above were not statistically significant. No severe adverse events appeared during the study period.

DISCUSSION

To the best of our knowledge, this study is the first randomized controlled study to compare risperidone and olanzapine in schizophrenic patients who have had neuroleptic-induced tardive dyskinesia. This study may provide more clear guidance for drug choices for patients with tardive dyskinesia.

Both risperidone and olanzapine significantly reduced dyskinesia, which was demonstrated in the changes in the

Table 1. Patient Demographic Data and Clinical Characteristics at Baseline Visit

Characteristic	Risperidone (n = 30)	Olanzapine (n = 30)	*P* Value[a]
Age, mean ± SD, y	42.7 ± 11.2	48.0 ± 11.9	.078
Male/female, n	10/20	11/19	.787
Duration of illness, mean ± SD, y	15.1 ± 9.3	16.8 ± 9.8	.508
Duration of antipsychotics treatment, mean ± SD, y	10.8 ± 8.2	10.5 ± 8.1	.872
Duration of tardive dyskinesia, mean ± SD, m	10.2 ± 14.8	15.5 ± 16.1	.184
AIMS total score, mean ± SD	17.2 ± 4.6	19.4 ± 6.1	.110
Global impression of ESRS, mean ± SD			
Dyskinesia	5.3 ± 1.2	5.4 ± 1.5	.926
Parkinsonism	3.5 ± 1.3	3.6 ± 1.2	.763
Dystonia	0.4 ± 1.3	0.4 ± 1.2	.920
Akathisia	1.5 ± 1.6	2.0 ± 2.1	.265
CGI-S, mean ± SD	4.5 ± 1.3	4.2 ± 1.1	.345
BPRS, mean ± SD	40.3 ± 11.0	35.9 ± 6.5	.123
Body weight, mean ± SD, kg	60.8 ± 15.0	60.8 ± 13.9	.999
CPE at screening visit, mean ± SD, mg/d	315.3 ± 226.9	374.8 ± 209.8	.296
Washout period, mean ± SD, d	3.7 ± 1.1	4.2 ± 1.40	.132

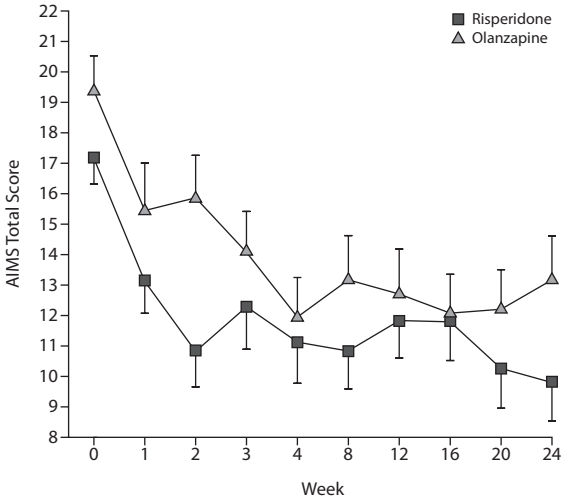
[a]Comparison between the risperidone and olanzapine groups.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CPE = chlorpromazine equivalent dose, ESRS = Extrapyramidal Syndrome Rating Scale.

Table 2. Between-Group Differences in Changes of Severity of EPS and Psychotic Symptoms From Baseline to End Point

Measure	Risperidone (n = 30)	Olanzapine (n = 30)	*P* Value[a]
AIMS total score, mean ± SD	−7.4 ± 6.9	−6.2 ± 8.0	.548
Global impression of ESRS, mean ± SD			
Dyskinesia	−1.7 ± 2.8	−1.4 ± 1.9	.552
Parkinsonism	0.1 ± 1.2	−0.6 ± 1.3	.022
Dystonia	0.4 ± 1.4	−0.3 ± 1.4	.049
Akathisia	−0.1 ± 1.4	−0.9 ± 2.3	.107
CGI-S, mean ± SD	−0.6 ± 1.3	−0.5 ± 1.5	.927
BPRS total score, mean ± SD	−4.4 ± 16.8	−2.7 ± 8.1	.633

[a]Comparison between the risperidone and olanzapine groups.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, EPS = extrapyramidal syndrome, ESRS = Extrapyramidal Syndrome Rating Scale.

Figure 2. The Progression of Abnormal Involuntary Movement Scale (AIMS) Total Scores From Baseline to End Point (last observation carried forward)[a]



[a]Tested by linear mixed model for repeated measurements. $P = .0001$.

Table 3. Adverse Events

Adverse Event, n (%)	Risperidone (n = 30)	Olanzapine (n = 30)	*P* Value[a]
Drowsiness	6 (20)	4 (13.3)	.488
Weakness	5 (16.7)	4 (13.3)	> .999
Dizziness	5 (16.7)	5 (16.7)	> .999
Headache	4 (13.3)	3 (10)	> .999
Palpitation	4 (13.3)	1 (3.3)	.353
Nausea	4 (13.3)	0 (0)	.112
Constipation	3 (10)	1 (3.3)	.612
Muscle ache	2 (6.7)	3 (10)	> .999
Thirst	2 (6.7)	3 (10)	> .999
Blurred vision	2 (6.7)	2 (6.7)	> .999
Psychotic symptoms worsening	1 (3.3)	2 (6.7)	> .999
Dyspnea	1 (3.3)	2 (6.7)	> .999
Postural hypotension	0 (0)	1 (3.3)	> .999

[a]Comparison between the risperidone and olanzapine groups.

AIMS total scores and global impression of ESRS dyskinesia after 24-week treatment. Contrary to our hypothesis, olanzapine did not have better efficacy in decreasing tardive dyskinesia severity than risperidone did. Instead, risperidone might be more effective than olanzapine in alleviating tardive dyskinesia. In our study, the high EPS liability of risperidone reflected a higher incidence of anticholinergic drug use than the olanzapine group and a slight increase in global impression of parkinsonism and dystonia from baseline to study end point. Fewer patients (6.7%) in the olanzapine group needed anticholinergic drugs, and they had slightly decreased scores on global impression of parkinsonism, dystonia, and akathisia. The differential effects of risperidone and olanzapine on EPS in this susceptible population seemed comparable to those general schizophrenic patients. The above observations were consistent with the fact that risperidone has stronger D_2 receptors antagonist effects and higher EPS side effects than olanzapine.[40,41]

There are significant between-group differences in the use of anticholinergic drugs to manage EPS. The effects of anticholinergic medications and cholinergic medications on tardive dyskinesia are still controversial. Some studies[42,43] have shown that anticholinergic medications might worsen tardive dyskinesia and cholinergic medications might improve tardive dyskinesia, but Cochrane systematic reviews[44,45] did not draw a definite conclusion and suggested further studies with sound study design to disclose this issue. Another point is that olanzapine had higher anticholinergic action than risperidone. Both are potential confounders of the treatment outcome. The influence of concomitant anticholinergic drugs in patients with tardive dyskinesia in the context of treatment with risperidone and olanzapine warrants further investigation.

In our study, however, there were no between-group differences in the change of tardive dyskinesia severity from

baseline to study end point. Two possible explanations are that risperidone also had high 5-HT_{2A} receptors antagonist effects, which may increase endogenous dopamine release,[46] to prevent the long-term complication of D_2 receptors blockade and that tardive dyskinesia is attributable to many etiologies so more than 1 mechanism can explain the results, such as dopamine receptors hypersensitivity.[47]

Some studies[48–50] have revealed that early parkinsonism or akathisia side effects of antipsychotics may predict future occurrences of tardive dyskinesia. The risperidone group did not show exacerbation of tardive dyskinesia at a later period in our study. This result is consistent with some previous studies.[38,51,52] But we still need to consider that the improvement of tardive dyskinesia might be due to the masked effect of risperidone and the deterioration of tardive dyskinesia after long-term treatment. Meanwhile, the AIMS total scores in the olanzapine group gradually increased from the 16th week to 24th week. There were also some case reports of olanzapine-induced or worsening tardive dyskinesia.[53,54] Previous studies[55] of tardive dyskinesia have shown that FGAs can decrease scores of dyskinesia. The symptomatic improvement may be due to masking effects of FGAs. Long-term effects of risperidone and olanzapine in a population with tardive dyskinesia need further investigation.

The washout period in our study was between 3 and 7 days, with a mean of about 4 days. On the contrary, previous studies' washout periods were about 2 to 4 weeks long.[15,16] Prolonged washout periods had the advantages of less carryover effect from previous antipsychotics and provided more reliable diagnoses and assessments for tardive dyskinesia. However, a prolonged washout period could worsen psychotic symptoms in schizophrenia patients and discourage patients from participation the study. Two patients in our study experienced exacerbation of psychotic symptoms during 7 days of washout and withdrew from the study. We can expect that longer washout periods may put more patients at risk for exacerbation of psychotic symptoms. Shorter washout periods also have the advantage of close to real clinical practice and increase external validity of this study.

The mean dose of risperidone with flexible-dose design was lower than that in the fixed-dose design study of 6 mg/d.[15] At the same time, our mean dose was slightly higher than the open-level study of Bai et al,[38] which had a mean dose of 3.6 mg/d. The mean dose of olanzapine in the Kinon et al[17] study was 12.1 mg/d, which was similar to our result. Further multidose comparison studies are needed to provide the evidence of optimal doses of risperidone and olanzapine for schizophrenia patients with tardive dyskinesia.

The degree of tardive dyskinesia improvement in the risperidone group was similar to but slightly higher than that in previous studies. AIMS total scores decreased by 5.5 in a 12-week study and by 6.1 in a 48-week study.[15,16] Tardive dyskinesia improvement in the olanzapine group was also higher than Kinon and colleagues'[17] study, whose AIMS total scores decreased by 4.5 in an 8-month period. Compared to previous studies, there were more decreases in AIMS total scores in both risperidone and olanzapine groups. This may be due to higher baseline AIMS total scores in our study population. Linear regression analysis showed that patients with higher baseline AIMS total scores had greater AIMS total score reduction (regression coefficient: −0.51, $P = .003$). This result is consistent with that of the Kinon et al[17] study.

Tardive dyskinesia improvement in both groups was most evident in the first 4 weeks, and then stabilized during the remaining study periods. This result was compatible with some of the previous studies on risperidone showing the most significant improvement was in the first 2 to 3 months of treatment.[38] Previous studies on olanzapine also showed that tardive dyskinesia improvement was most evident in the first few weeks, reaching maximum improvement in the 20th week.[17] Nevertheless, the results from some studies on quetiapine and clozapine revealed that tardive dyskinesia improvement could persist up to 9 months or even 1 year.[12,16] Clozapine and quetiapine had the mechanism of fast dissociation and might exhibit a different improvement profile.[56] If we use more than 50% improvement in severity of tardive dyskinesia from baseline to study end point as the definition of *responder*, the proportion of responders in our study was similar to that in a clozapine study[13] (43%) but lower than that in a quetiapine study (64% and 55% at 6 months and 1 year, respectively).[16] Nevertheless, due to different tardive dyskinesia populations and study designs, it would be difficult to directly compare results from this and previous studies. Head-to-head comparison studies of different SGAs are still warranted to make a straightforward comparison and interpretation.

There were some limitations to our study. First, we did not have an FGA or placebo control group due to ethical concerns. Hence, the study result might be confounded by placebo effect and thus overestimated the effects of SGA on improving FGA-induced tardive dyskinesia. Second, our study was a rater-blinded study in which primary care physicians and patients were not blinded. Thus, the result may be influenced by measurement bias. Third, the results of our studies were limited by small sample size and inadequate power to detect the between-group differences. In addition, small sample size also weakens the effects of randomization to balance the potential confounder distribution. Fourth, our study was a 24-week study, so our results cannot be applied to patients receiving long-term treatments. Fifth, our study was a flexible-dose study, so we cannot directly infer our results to those of fixed-dose studies on risperidone and olanzapine. In addition, there may be a possibility of inadequate dose titration in some patients. Finally, our study did not perform laboratory tests, so we could not assess the patients' blood sugar levels, triglyceride, prolactin, and other biochemical data.

In summary, although our study had above limitations, the results have some clinical implications for clinicians: (1) Although olanzapine had fewer EPS side effects than risperidone in general, olanzapine did not show superior

efficacy to risperidone in a tardive dyskinesia population. (2) Tardive dyskinesia may be a heterogeneous condition and cannot be explained by a single hypothesis, such as dopamine receptor hypersensitivity. More studies focusing on tardive dyskinesia populations are recommended to help clinicians make appropriate clinical decisions.

Drug names: clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).
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Potential conflicts of interest: **Drs Chan** and **Chang** have received speech honoraria from Astellas, AstraZeneca, Eli Lilly, Janssen, Otsuka, Pfizer, and SanofiAventis. **Drs Chiang**, **Gau**, **J.-J. Chen**, **C.-H. Chen**, **Hwu**, and **Lai** report no potential conflicts of interest relevant to the subject of this article.
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