Risperidone for Severe Tardive Dyskinesia: A 12-Week Randomized, Double-Blind, Placebo-Controlled Study

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Background: Risperidone has been reported to alleviate the severity of tardive dyskinesia, but without placebo control, the possibility of spontaneous tardive dyskinesia remission after discontinuing original conventional antipsychotics cannot be excluded. This 12-week randomized, double-blind, placebo-controlled study investigated the effect of risperidone on severe tardive dyskinesia.

Method: Forty-nine DSM-IV schizophrenia patients with severe tardive dyskinesia were enrolled in the study. After a 4-week washout period, the subjects were randomly assigned to treatment with either risperidone or placebo. The risperidone dose was started at 2 mg/day and gradually increased to 6 mg/day over 6 weeks; the 6-mg/day dose was maintained for the remaining 6 weeks of the study. The subjects were evaluated every 2 weeks with the Abnormal Involuntary Movement Scale (AIMS) and the Extrapyramidal Symptom Rating Scale. The final mental status was assessed with the Brief Psychiatric Rating Scale.

Results: Twenty-two subjects in the risperidone group and 20 subjects in the placebo group completed the study; the mean baseline AIMS total score for all subjects was 15.9 ± 4.6. At the end of the study, the mean AIMS total score decrease was 1.1 ± 4.8 in the placebo group and 5.5 ± 3.8 in the risperidone group ($p < .05$). Fifteen subjects (68%) in the risperidone group and 6 subjects (30%) in the placebo group were responders ($p < .05$). The risperidone responders had a mean AIMS total score decrease of 7.5 ± 2.1. More significant tardive dyskinesia improvement among the risperidone group was noted from the eighth week and was mainly demonstrated in the buccolinguomasticatory a rea rather than in choreoathetoid movement of the extremities ($p < .001$).

Conclusions: Risperidone, 6 mg/day, can improve tardive dyskinesia more significantly than discontinuing antipsychotics in patients with severe tardive dyskinesia, especially in the orofacial areas.

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Tardive dyskinesia is a serious and potentially irreversible side effect with long-term use of conventional antipsychotics. The incidence of new tardive dyskinesia is 3% to 5% per year, and a cumulative incidence of 30% to 50% may be reached after 5 to 10 years of conventional antipsychotic treatment.[1,2] The typical course of tardive dyskinesia is gradual onset after several years of drug therapy. A reduction in movements or full remission may occur in approximately 10% to 30% of cases, with some degree of further worsening taking place in another 10% to 30%, approximately. Thus, a large number of patients have persistent tardive dyskinesia with irreversible symptoms.[3,4] Treatment for tardive dyskinesia remains empirical, and at present, there is no standard and uniform modality.[3] When tardive dyskinesia is diagnosed, clinicians may consider reducing the dosage of dopamine antagonist or stopping the medication altogether if the psychiatric condition is feasible.[5,6] But some patients have persistent tardive dyskinesia for years after discontinuing neuroleptic regimens.[7]

Second generation antipsychotics (SGAs) have been reported to be associated with much lower incidence of tardive dyskinesia,[3,8–13] and there is emerging literature in support of treatment for existing drug-induced movement disorder.[3,10–17] Clozapine was the first SGA reported to effectively alleviate tardive dyskinesia, especially in those with dystonic features.[18–20] But the risk of agranulocytosis and the necessity of frequent hematologic monitoring limited clozapine use.[18]

Risperidone has been reported to improve tardive dyskinesia in many case reports, as well as in some open-label studies.[21–32] Williams et al.[24] reported a significant reduction in tardive dyskinesia in 20 schizophrenia patients taking 6 mg/day of risperidone in a 13-week trial. Khan[25] reported a rapid, significant, and persistent

improvement in tardive dyskinesia with risperidone, 3 to 6 mg/day, for 13 developmentally disabled patients in a 1-year trial. Jeste et al.[29] reported that 59 elderly patients with dyskinetic symptoms experienced significant and persistent reductions in the severity of tardive dyskinesia with risperidone treatment for 1 year. Megna and Dewan[33] reported that 10 patients with severe and treatment-resistant mental illness, who all had tardive dyskinesia at baseline, experienced improvement of tardive dyskinesia with approximately 14 months of risperidone treatment. A 1-year study by Chen et al.[27] also showed the persistent antidyskinetic effect of risperidone in some cases.

But because the course of tardive dyskinesia fluctuates[3,4] and approximately a third of tardive dyskinesia cases improved by more than 50% within 3 months of discontinuation of neuroleptics,[34] the possibility of rating bias and spontaneous remission after withdrawal from the original conventional antipsychotic cannot be excluded for many open-trial studies.[24,25,27,29,33] As Megna and Dewan suggested,[33] because tardive dyskinesia improvement was noted within the first 3 months of risperidone treatment, such improvement was more likely secondary to withdrawal of the typical antipsychotic than to a direct effect of risperidone. Chouinard[22] reported the only double-blind, placebo-controlled study, with 135 schizophrenia inpatients randomly assigned to 6 treatment groups for 8 weeks; risperidone, 2, 6, 10, 16 mg/day; haloperidol, 20 mg/day; or a placebo was administered. A post hoc analysis showed that risperidone, 6 mg/day, had the most beneficial effect on tardive dyskinesia for 49 patients. The main limitation of that study[22] was the short 8-week study period, because withdrawal tardive dyskinesia takes 12 weeks to subside.[34,35]

Considering that spontaneous remission of tardive dyskinesia after withdrawal of neuroleptic medication usually occurs within 3 months,[34] and 6 mg/day has been suggested as the most efficacious dose of risperidone to improve tardive dyskinesia,[22,27] we designed a 12-week randomized, double-blind, placebo-controlled study to explore the effect of risperidone, 6 mg/day, on tardive dyskinesia. The study design included sufficient duration to avoid the confounding effect of withdrawal tardive dyskinesia, provided a placebo control to exclude the possibility of spontaneous remission after withdrawal of the original antipsychotic, and used a double-blind design to avoid rating bias and successive ratings to investigate the course of tardive dyskinesia severity changes. Considering the possibility of different therapeutic responses to different severities of tardive dyskinesia, we recruited patients with severe tardive dyskinesia as a target sample. Severe tardive dyskinesia causes patients more serious appearance disfigurement and social consequences. The study results will be particularly valuable as a clinical reference.

METHOD

Forty-nine hospitalized chronic DSM-IV schizophrenia patients with persistent severe tardive dyskinesia participated in this 12-week randomized, double-blind, placebo-controlled study. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Yu-Li Veterans Hospital. The study was completely described to all patients, and all patients provided written informed consent.

Severe tardive dyskinesia was defined as severe, abnormal, involuntary movement noted in 1 or more of 7 body areas (face, lips, jaw, tongue, upper extremities, lower extremities, and trunk) or moderate movement in 2 or more areas. The criteria were more stringent than Schooler and Kane's[36] research diagnostic criteria for tardive dyskinesia, which require only moderate abnormal involuntary movement in 1 or more body areas or mild movement in 2 or more areas. Every eligible subject was rated twice within a 3-month interval to meet the criteria of persistent tardive dyskinesia. Other inclusion criteria included: (1) age between 18 and 65 years, (2) maintenance on conventional antipsychotics for more than 1 year with an equivalent dosage of less than 200 mg/day of chlorpromazine, (3) Brief Psychiatric Rating Scale (BPRS)[37] total scores of less than 20, and (4) no record of any violent or aggressive behavior within the last 6 months, to minimize the risk of psychotic exacerbation after withdrawing antipsychotics. The exclusion criteria were (1) comorbidity of organic mental disorder or major physical illness, (2) ever being prescribed any atypical antipsychotic, and (3) neuroleptic depot administration within the last 6 months.

Tardive dyskinesia was assessed by 3 investigators using a standardized Abnormal Involuntary Movement Scale (AIMS)[38] examination procedure. Before the study, AIMS interrater reliability assessment was performed for 60 ratings. The interrater reliability for the 7-item AIMS total score was 0.94, which was derived from the intraclass correlation coefficient analysis of variance.

The baseline tardive dyskinesia severity, other extrapyramidal side effects, and psychiatric symptoms were assessed with the AIMS, the Extrapyramidal Symptom Rating Scale (ESRS),[39] and the BPRS, respectively. After a 4-week washout period with all original conventional antipsychotics discontinued, subjects were randomly assigned to the risperidone or placebo groups. In the risperidone group, the risperidone dose was started at 2 mg/day and increased, with a 2-mg increase every 2 weeks, to 6 mg/day over 6 weeks; the 6-mg/day dose was maintained for the remaining 6 weeks of the study. A placebo with an identical appearance to the risperidone dose was prescribed for the placebo group using the same dose schedule. During the study period, the assessment of tardive

Table 1. Demographic Data, Rating Scale Scores, and Conjunctive Benzodiazepine and Anticholinergic Use for Risperidone and Placebo Groups

Characteristic	Risperidone Group (N = 22)	Placebo Group (N = 20)	Significance
Age, mean ± SD, y	49.1 ± 10.2	51.4 ± 9.1	NS
Male, N (%)	16 (73)	12 (60)	NS
Hospitalization duration, mean ± SD	13.6 ± 10.9	10.0 ± 9.0	NS
BPRS score, mean ± SD			
Baseline	13.2 ± 4.9	13.7 ± 6.1	NS
Final	14.7 ± 7.4	19.0 ± 12.2	NS
ESRS-parkinsonism score, mean ± SD			
Baseline	2.6 ± 1.6	2.8 ± 1.4	NS
Final	2.1 ± 1.3	2.5 ± 1.5	NS
ESRS-dystonia score, mean ± SD			
Baseline	1.6 ± 2.1	2.0 ± 2.0	NS
Final	2.1 ± 1.7	2.8 ± 1.8	NS
AIMS score, mean ± SD			
Baseline	15.4 ± 5.0	16.4 ± 4.3	NS
Final	9.9 ± 4.4	15.4 ± 5.7	Mann-Whitney U test, 2-tailed, p = .002
Responders, N (%)	15 (68)	6 (30)	Fisher 2-sided, p = .029
Cases with benzodiazepine use, N (%)	19 (86)	18 (90)	NS
Cases with antiparkinsonism drug use, N (%)	14 (86)	10 (50)	NS

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, ESRS = Extrapyramidal Symptom Rating Scale, NS = not significant.

dyskinesia severity and other extrapyramidal side effects was performed every 2 weeks until the end of the study. The final mental status was assessed with the BPRS. All tardive dyskinesia evaluations were performed in the afternoon after patients had been awake for more than 2 hours to avoid the confounding effect of diurnal variation.[36] The administration of other antipsychotics (oral or injected) was prohibited during the 12-week study period. The anticholinergics were titrated according to the extrapyramidal side effects, and benzodiazepines could be prescribed adjunctively if the patient's psychiatric condition was unstable. Participation in the study was discontinued if the psychotic symptoms were exacerbated or the side effects of risperidone were not tolerated.

Schooler and Kane's[36] research diagnostic criteria for tardive dyskinesia require an AIMS total score of at least 3 or 4. We defined a subject with an AIMS total score decrease of at least 3 or 4 as a responder,[27] representing clinically observable improvement. The outcome analysis was based on the intent-to-treat sample. Nonparametric Mann-Whitney U test was used to compare score change between the 2 groups, and Wilcoxon signed rank test was used for intragroup baseline and outcome comparisons. Linear regression analysis was used for AIMS and ESRS correlation statistics. For all comparisons, the level of significance was set at .05. SPSS 10.0 for Windows (SPSS Inc., Chicago, Ill.) was used for the statistical analysis.

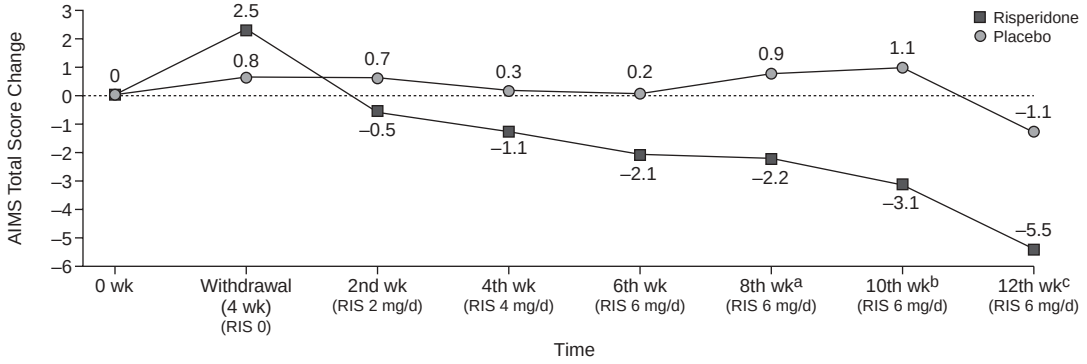
RESULTS

Forty-two patients completed the 12-week study and 7 subjects withdrew. Four subjects dropped out due to psychotic symptom exacerbation (2 subjects during the washout period: 1 subject in the placebo group and 1 subject in the risperidone group). Another 3 subjects withdrew due to a medical condition (infectious disease, heart condition, and lung carcinoma). The mean age of all 42 subjects was 50.2 ± 9.6 years. Twenty-eight subjects were male (66.7%). For all subjects, the mean hospitalization duration was 11.86 ± 10.1 years, the mean baseline AIMS total score was 15.9 ± 4.6, and the mean baseline BPRS score was 13.4 ± 5.4.

The final sample consisted of 22 subjects in the risperidone group and 20 subjects in the placebo group. There was no significant difference between the 2 groups for the variables of age, gender, hospitalization duration, or AIMS, BPRS, and ESRS scores at baseline. No significant differences in ESRS scores or the percentage of concomitant antiparkinsonism and benzodiazepine use were noted between the 2 groups at the end of the study. More significant mean AIMS total score decrease was noted in the risperidone group (5.5 ± 3.8) than in the placebo group (1.1 ± 4.8) ($t = 3.3$, $df = 40$, $p = .001$). Significantly more responders were noted among the risperidone group (15 subjects, 68%) than the placebo group (6 subjects, 30%) (Fisher exact test, 2-sided, $p = .029$) (Table 1). The significant difference of change in AIMS total score between the 2 groups was noted from the eighth week, and the difference became more distinct with time (Figure 1). The significant tardive dyskinesia improvement among the risperidone group was shown mainly in the buccolinguomasticatory (BLM) area rather than in choreoathetoid movement of the extremities (Table 2).

There was no significant difference in ESRS score change between the 2 groups, and no correlation was

Figure 1. Course of AIMS Total Scores Change in the Risperidone and Placebo Groups



[a]The difference in the decrease in AIMS scores between the 2 groups at the 8th week: Mann-Whitney U test, 2-tailed, p = .018.
[b]The difference in the decrease in AIMS scores between the 2 groups at the 10th week: Mann-Whitney U test, 2-tailed, p = .008.
[c]The difference in the decrease in AIMS scores between the 2 groups at the 12th week: Mann-Whitney U test, 2-tailed, p = .003.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, RIS = risperidone.

Table 2. Comparison of Change (mean ± SD) in AIMS Subscores Between the Risperidone and Placebo Groups

Item	Risperidone Group (N = 22)	Placebo Group (N = 20)	Mann-Whitney U Test, 2-Tailed, p Value
1: Facial expression muscles	–1.4 ± 1.2	0.03 ± 1.1	p = .001
2: Lips and perioral area	–0.7 ± 0.9	–0.2 ± 1.3	NS
3: Jaw	–0.5 ± 1.5	0.2 ± 1.3	NS
4: Tongue	–1.7 ± 1.0	0.2 ± 1.3	p = .000
5: Upper extremities	–0.4 ± 1.0	–0.1 ± 1.3	NS
6: Lower extremities	–0.4 ± 1.5	–0.7 ± 1.3	NS
7: Neck, shoulder, hips	–0.4 ± 0.8	–0.3 ± 1.6	NS

Table 3. Change (mean ± SD) in AIMS and ESRS Scores Among the Risperidone and Placebo Groups at Each Follow-Up[a]

	Risperidone			Placebo		
Follow-Up	AIMS Total Score Change	Parkinsonism Score Change	Dystonia Score Change	AIMS Total Score Change	Parkinsonism Score Change	Dystonia Score Change
Washout	2.47 ± 4.1	–1.0 ± 1.3	0.7 ± 1.8	0.78 ± 4.7	–1.0 ± 1.5	–0.1 ± 1.8
2nd week	–0.46 ± 5.1	–0.9 ± 1.6	0.3 ± 2.0	0.67 ± 4.4	–1.1 ± 1.4	–0.5 ± 1.8
4th week	–1.10 ± 5.4	–1.1 ± 1.4	–0.2 ± 2.0	0.28 ± 4.7	–1.3 ± 1.8	–0.6 ± 2.1
6th week	–2.10 ± 4.7	–1.3 ± 1.2	0.0 ± 2.5	0.20 ± 4.8	–1.3 ± 1.9	0.3 ± 1.7
8th week	–2.20 ± 4.7	–0.7 ± 1.6	–0.5 ± 2.0	0.94 ± 4.8	–1.4 ± 1.8	0.0 ± 2.1
10th week	–3.10 ± 4.6	–0.9 ± 1.5	–0.1 ± 2.0	1.10 ± 5.2	–1.0 ± 1.8	–0.5 ± 2.1
12th week	–5.50 ± 3.8	–0.5 ± 1.5	0.4 ± 1.8	–1.10 ± 4.8	–0.6 ± 1.5	0.5 ± 1.6

[a]No significant correlation was noted between AIMS total score and ESRS-parkinsonism change (r = –0.324, df = 12, p = .119), or AIMS and ESRS-dystonia change (r = –0.046, df = 12, p = .825) at each follow-up.

noted between change in AIMS scores and ESRS-parkinsonism or ESRS-dystonia scores at each follow-up (Table 3).

DISCUSSION

This study is the first to focus on severe tardive dyskinesia, and the results show that severe tardive dyskinesia can be improved with risperidone, 6 mg/day. More than two thirds of subjects in the risperidone group were responders with an average decrease in the AIMS total score of 7.5 ± 2.1. The improvement is consistent with Khan's[25] result of a 7.3 ± 4.3 decrease and a 7.0 ± 2.7 decrease result reported by Chen et al.[27] The control function of the placebo group indicated that the improvement was significant and not confounded by withdrawal tardive dyskinesia or spontaneous remission after withdrawal of the original neuroleptics.

Previous reports[34,35,40,41] indicated that an increase of tardive dyskinesia severity would be noted after decreasing the dosage of conventional antipsychotics. The withdrawal tardive dyskinesia was most significant within 1 or 2 weeks and usually subsided within 3 months. Our results were consistent with those reports.[34,35,40,41] All

patients showed an increased AIMS score during the 4-week washout period and then a mildly fluctuated course, with a nonsignificant increase of AIMS scores noted in the placebo group. At the 12th week, the improvement of tardive dyskinesia was evident, and 6 subjects (30%) in the placebo group were noted as responders. This result was consistent with Jeste's report[29] that approximately a third of TD cases improved by more than 50% within 3 months of discontinuation of neuroleptics. We suggest that a response rate of more than 30% would be necessary for a positive tardive dyskinesia study result.

In the risperidone group, the tardive dyskinesia severity decreased continuously during the study period. The statistically significant tardive dyskinesia improvement was noted in the risperidone group from the eighth week compared with the placebo group, and the difference became more distinct with time. The rapid improvement was consistent with reports by Khan[25] and Megna and Dewan[33] that improvement was most noted within 2 to 3 months. Overall, 3 patients had psychotic symptom relapse after discontinuation of antipsychotics, although they were part of a selected group with relative lower risk of relapse according to the inclusion criteria. In a 40-week follow-up study by Glazer et al.,[7] complete remission of tardive dyskinesia was rare (2%) with neuroleptic discontinuation; the severity decreased in only 20%, but the rate of psychosis relapse approached 50%. Our results supported the finding that complete discontinuation of antipsychotic medication is not a viable alternative in patients with schizophrenia, even in those with severe tardive dyskinesia.

The pathophysiology of tardive dyskinesia is still unknown. The dopamine hypersensitivity theory with D_2 receptor up-regulation is most directly related to the long-term neuroleptic action[4]; 5-HT_{2A} antagonism can reduce D_2 antagonism. Manipulation of the serotonin system through the use of atypical antipsychotics may contribute to an alteration in the balance between the dopamine and serotonin systems in the basal ganglia and reduce the symptoms of dyskinesia.[13,42,43] Risperidone can be considered for patients with tardive dyskinesia as a useful alternative to clozapine, which is known to have serious side effects such as agranulocytosis and epilepsy.[24] For patients with severe tardive dyskinesia, switching to risperidone is a safer and more effective treatment modality than merely discontinuing original conventional antipsychotics.

For comparison with previous positive studies of risperidone for tardive dyskinesia, we used 6 mg/day as the target dose, which was a relatively higher equivalent dosage than those of the original conventional antipsychotics used by our subjects. Was the improvement in tardive dyskinesia an active therapeutic effect or just a mask effect? Our results showed that the ESRS-parkinsonism score was decreased among all subjects, and no correlation of AIMS and ESRS score changes was noted in either group, which was consistent with the report by Jeste et al.[29] Jeste et al.'s[29] report and our results may partially support the notion that tardive dyskinesia improvement is not due to suppressive effects, otherwise an increase in parkinsonism scores would be noted. Of course, the best way to resolve the question is through long-term follow-up. Studies by Khan,[25] Jeste et al.,[29] and Chen et al.[27] showed that the antidyskinetic effect of risperidone was not a short-term effect and could persist for 1 year. Khan[25] suggested that risperidone had a therapeutic effect rather than a mask effect on tardive dyskinesia, otherwise the tardive dyskinesia symptoms would have reappeared during such a long-term follow-up.

The antidyskinetic effect rather than the mask effect is also supported by clozapine studies. Gerbino et al.[44] reported that 24 tardive dyskinesia patients treated with clozapine showed at least a 50% reduction in severity of tardive dyskinesia, and no recurrence of tardive dyskinesia was observed within 1 year. Lieberman et al.[18] reported that approximately 43% of tardive dyskinesia cases responded to clozapine with an "active therapeutic effect," because the improvement in tardive dyskinesia remained without recurrence during clozapine treatment for almost 2 years. Tamminga et al.[19] reported that clozapine produced significantly greater benefit for tardive dyskinesia than did haloperidol in a 1-year study. Moreover, the tardive dyskinesia rebound was sustained in the haloperidol group but lost in clozapine-treated patients. They proposed that patients with tardive dyskinesia lose their symptoms and dopaminergic hypersensitivity with long-term clozapine treatment.[19] These studies[18,19,44] suggest an active therapeutic effect of tardive dyskinesia with SGAs. But further studies are greatly needed to investigate the long-term effect of risperidone on tardive dyskinesia, and whether tardive dyskinesia symptoms reemerge when the risperidone dosage is reduced or withdrawn.

Our results showed that significant tardive dyskinesia improvement with risperidone is most pronounced for the BLM area and less so for choreoathetoid movement in the extremities, which is consistent with Chouinard's report.[22] It has been suggested that BLM and choreoathetoid tardive dyskinesia be grouped as 2 syndromes.[22] For instance, a history of alcohol abuse or dependence is a significant predictor for BLM tardive dyskinesia only, whereas tremors are a significant predictor for choreoathetoid tardive dyskinesia only. A recent change in neuroleptic dose has a direct effect on choreoathetoid tardive dyskinesia, but not on BLM tardive dyskinesia.[45] BLM tardive dyskinesia is more prevalent in older patients, whereas choreoathetoid tardive dyskinesia is more prevalent in younger patients.[46] Different incidence rates have also been noted among the 2 syndromes.

In general, approximately 70% to 100% of tardive dyskinesia patients manifest orofacial movements, 20% to

60% limb-truncal movements, and 11% to 50% both orofacial and limb-truncal movements.[5] Our results revealed that BLM and choreoathetoid tardive dyskinesia respond differently to risperidone, further supporting the recommendation to group them as 2 syndromes. Differences in BLM and choreoathetoid tardive dyskinesia should be considered when selecting cases and evaluating outcomes in future studies.

Because the risk of psychotic symptom relapse may increase with time, the placebo group could not be maintained for longer than 12 weeks. Although the respective long-term antidyskinetic effects of risperidone treatment and neuroleptic discontinuation remain unknown, the latter is more risky for relapse, and not a viable alternative for chronic schizophrenia patients with tardive dyskinesia. There are an increasing number of reports about tardive dyskinesia improvement with other SGAs, such as olanzapine and quetiapine[47–63]; most are case reports, and the study periods were not long enough to adequately show the effect of SGAs on tardive dyskinesia. At the same time, all SGAs have been reported to induce tardive dyskinesia.[64–69] The mechanism of tardive dyskinesia still remains inconclusive, and tardive dyskinesia usually appears after years of treatment; the longest study of SGAs for tardive dyskinesia was approximately 1 year. More long-term studies are required to investigate the safety of SGAs and their effect on tardive dyskinesia.

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

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