Extract of *Ginkgo biloba* Treatment for Tardive Dyskinesia in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Objective:** Free radicals may be involved in the pathogenesis of tardive dyskinesia (TD). Extract of *Ginkgo biloba* (EGb) is a potent antioxidant possessing free radical-scavenging activities. The aim of the study was to evaluate the efficacy of EGb-761, a standardized extract given in capsule form, in treating TD in schizophrenia patients. **Method:** Inpatients with DSM-IV–diagnosed schizophrenia and TD (n = 157) in a mainland China Veterans Affairs psychiatric hospital were randomly assigned to 12 weeks of treatment with either EGb-761, 240 mg/d (n = 78) or a placebo (n = 79) in a double-blind manner. Primary outcome measures were (1) change from baseline in the Abnormal Involuntary Movement Scale (AIMS) score and (2) proportion of patients with a ≥ 30% reduction in their AIMS total score at week 12. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS) and cognitive performance as measured by the Continuous Performance Test-37 Version and the 3-card Stroop task. Patients were recruited for the study between December 2006 and May 2007. **Results:** Of the 157 patients who were randomly assigned, 152 (96.8%) completed the study. EGb-761 treatment significantly decreased the AIMS total score in patients with TD compared to those who were given a placebo (2.13 ± 1.75 vs −0.10 ± 1.69; *P* < .0001), with 40 (51.3%) and 4 (5.1%) patients achieving response in the EGb-761 and placebo treatment groups, respectively. There were no between-group differences in the PANSS total score or cognitive measures from baseline to week 12. **Conclusions:** EGb-761 appears to be an effective treatment for reducing the symptoms of TD in schizophrenia patients, and improvement may be mediated through the well-known antioxidant activity of this extract. **Trial Registration:** clinicaltrials.gov identifier: NCT00672373

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Tardive dyskinesia (TD) is a serious adverse effect associated with the long-term administration of neuroleptic medicine. Although the prevalence of TD can be reduced with atypical antipsychotics, it remains a risk in susceptible populations even with these agents. In addition, most patients in Third-World countries and up to half of European patients are still treated with typical antipsychotics. Although a large number of medications have been investigated for the treatment of patients with TD, no uniformly effective treatment has yet been established. This disorder may remain a significant clinical problem for the foreseeable future.

The pathophysiology of antipsychotic-induced TD is still unclear, although several reports have indicated that free radicals may be involved. Preclinical studies suggest that many antioxidants are associated with attenuated vacuous chewing movements in rats given typical antipsychotics. On the basis of the free radical hypothesis of TD, many antioxidants have been studied for the treatment of patients with this disorder, including vitamin E, vitamin B6, piracetam, and melatonin. So far, the most widely used antioxidant strategy has involved vitamin E. A meta-analysis of published studies showed that a significant subgroup (28.3%) of patients with TD who were treated with vitamin E showed modest improvement. In contrast, however, other studies have found that vitamin E has no effect in patients with the disorder. A newer Cochrane review showed that vitamin E protects against deterioration of TD, but there is no evidence that vitamin E improves symptoms of TD. The role of this vitamin in the treatment of TD remains unclear, although the dose studied so far does not appear to be clinically effective, especially for patients with long-standing TD.

EGb-761 is a standardized extract of *Ginkgo biloba* leaves that has antioxidant properties as a free radical scavenger. In the 1950s, the Dr Willmar Schwabe phytopharmaceutical company of Germany developed a concentrated, standardized form of extract of *Ginkgo biloba* (EGb) referred to as EGb-761. EGb-761 has 24% flavonoids (including monosides, biosides, and trisides of quercetin, isorhamnetins, 3′-O-methylmyristicins, and kaempferol) and 6% terpenes (including the diterpenes ginkgolide A, B, and C and the sesquiterpene bilabolido) with less than 5 ppm of ginkgolic acids. Because the components of *Ginkgo biloba* are fat-soluble, they are among the few dietary antioxidants that can readily cross the blood-brain barrier and protect the brain. EGb-761 has been widely used to treat cerebrovascular and peripheral vascular insufficiency, as well as the cognitive and functional symptoms associated with mild to moderate dementia. The antioxidant properties and free radical-scavenging actions of EGb-761 have been proposed to underlie its beneficial effects. On the other hand, this product has been found to have effects on neurotransmitter function. For example, a study reported that EGb-761 treatment produced a functional activation of cholinergic...
nerve terminals in the hippocampus in old rats. Also, it was found that EGb-761 at very low concentrations enhanced synaptosomal serotonin (5-HT) uptake similar to the antidepressant drug tianeptine. Our previous study showed that EGb-761 enhanced the effectiveness of the antipsychotic drug haloperidol and reduced its extrapyramidal side effects. To examine whether this extract is effective in the treatment of TD, we conducted a 12-week, randomized, double-blind, placebo-controlled trial in 157 male schizophrenia patients with TD. A 6-month follow-up was also conducted in the EGb-761 treatment group. We hypothesized that there would be significant improvement in the patients treated with EGb-761 as compared to the placebo group. Moreover, given the empirical evidence of cognitive improvement in patients with mild to moderate dementia after treatment with EGb-761, we hypothesized that patients with schizophrenia who received the treatment would also demonstrate corresponding cognitive improvement as compared to the placebo group.

METHOD

Participants

Between December 2006 and May 2007, 171 schizophrenic inpatients with TD were recruited at the Hebei Province Rong-Jun Hospital, a Veterans Affairs psychiatric hospital in mainland China. All of the subjects were male and satisfied the following inclusion criteria: (1) aged from 18 to 60 years old; (2) DSM-IV diagnosis of schizophrenia; (3) diagnosis of TD based on the Schooler-Kane criteria, that is, at least 1 Abnormal Involuntary Movement Scale (AIMS) item rated > 3 or at least 2 items rated > 2, confirmed independently by 2 trained psychiatrists; (4) a stable dose of antipsychotics for at least 4 weeks prior to trial entry; (5) symptom duration of at least 1 year; and (6) hospitalization for treatment. The exclusion criteria included (1) any neurologic disorder other than TD, (2) alcohol or drug abuse within the previous 6 months, (3) use of any antioxidants within the past 12 weeks, and (4) serious physical illness.

The patients were screened and given a complete clinical evaluation, including medical and neurologic examinations and laboratory tests, before they were included in the study. The study was approved by the Institute Review Board Committees of the Beijing Hui-Long-Guan Hospital and the Hebei Province Rong-Jun Hospital. Written informed consent was obtained from the subjects prior to entry after they had been provided with a detailed explanation of the study. The trial was registered with ClinicalTrials.gov (NCT00672373).

Study Design

The clinical trials consisted of a 1-week, single-blind placebo run-in followed by 12 weeks of double-blind treatment. The EGb-761 group of patients was followed up for 6 months.

On day 7, those patients who had 25% or greater improvement in their AIMS total scores following the 1-week, single-blind placebo treatment were removed from further study. After the run-in period, patients were randomly assigned to receive either capsulized EGb-761 (Yi Kang Ning; Yang Zi Jiang Pharmaceuticals Ltd, Jiangsu, China) or an identically capsulized placebo in a double-blind manner. In addition to their regular antipsychotic medication, the patients were given either 1 capsule (80 mg) of EGb-761 tid (240 mg/d) or 1 capsule of the placebo tid for 12 weeks. A previous study showed that systemically administered EGb-761 at 240 mg/d could influence electroencephalogram results. Furthermore, another study confirmed the clinical efficacy of EGb-761 of 240 mg/d as therapy for “mild-to-moderate” dementia of the Alzheimer's type and multi-infarct dementia. Therefore, EGb-761 was used at a dose of 240 mg/d in the current study.

Neuroleptics and all other medications remained fixed throughout the double-blind period. The medications that patients had been taking were clozapine (66 patients in the EGb-761 group vs 62 patients in the placebo group), risperidone (2 in EGb-761 vs 5 in placebo), aripiprazole (1 in EGb-761 vs 3 in placebo), olanzapine (2 in EGb-761), quetiapine (2 in EGb-761 vs 1 in placebo), chlorpromazine (2 in EGb-761 vs 4 in placebo), haloperidol (2 in EGb-761), or sulpiride (1 in EGb-761 vs 4 in placebo). Their chlorpromazine-equivalent doses were 429.3 and 440.2 mg/d in the EGb-761 and placebo groups, respectively. Anticholinergics were allowed during the trial. Twenty-seven patients (12 in the EGb-761 group and 15 in the placebo group) were treated with anticholinergics for a long time prior to entering the study; however, anticholinergic treatment was stable during the clinical trial. No new use of anticholinergic drugs was allowed. All study and routine medications were taken by the participants in the presence of nursing staff.

Randomization

Patients had an equal probability of being assigned to the 2 groups. An independent third party placed them in either the active or placebo group according to a computer-generated randomization list compiled through simple randomization. To ensure the concealment of allocation, this third party used a protected computer database for the randomization list. All of the study personnel and participants were blinded to the treatment assignment for the duration of the double-blind period, except 1 study staff member in the pharmacy, who remained unblinded to provide the placebo and EGb-761 treatments.

Assessment and Outcomes

The baseline assessments included demographics, comprehensive medical histories, and laboratory examinations, including liver and renal function, blood routine, and electrocardiogram. The primary outcome measure was the severity of TD symptoms, which was measured by the AIMS total score (the sum of items 1–7). The AIMS is generally accepted as an outcome measure that is sensitive to changes in TD in pharmacologic trials and has well-described psychometric properties. Patients with 30% or greater reduction in their AIMS total score were classified as having had a response.
Psychopathology was measured by the total Positive and Negative Syndrome Scale (PANSS) score and the positive, negative, and general psychopathology subscale scores. The secondary outcomes also included the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale and cognitive function. Cognitive performance improvements were measured by the Continuous Performance Test-37 (CPT-37) Version and the 3-card Stroop task.

The AIMS, PANSS, and UKU and laboratory examinations were conducted at baseline, week 6, and week 12. The cognitive function measurements were taken at baseline and at week 12. To ensure the consistency and reliability of ratings across the study, 3 psychiatrists who had worked for at least 5 years in clinical practice simultaneously attended a training session on the use of the scales before the start of the study. Each subject was assessed by the same investigator, who was blind to treatment status. After training, correlation coefficients for the AIMS and PANSS were 0.92 and 0.86 by repeated assessment, respectively.

The CPT-37 version, a variant of the CPT-AX (version 3.05 of ERTSCODE for MS-DOS, Berisoft Cooperation, Frankfurt, Germany), was administered to all of the participants on a personal computer. The digit 7, which appeared following the digit 3, was presented as the target stimulation. The digit 7, when it did not follow the digit 3, was presented as a false alarm (40 stimuli-pairs). The Stroop effect was computed as the reaction time difference in the experimental condition (naming the ink color of incongruently colored word colors) relative to the control condition (undistracted color naming). All of the tests were performed by a psychometric operator.

After 12 weeks of treatment, EGb-761 was discontinued. Patients in the EGb-761 group were followed up for 6 months to investigate any changes in TD symptoms via AIMS at weeks 18, 24, and 36. The 6-month extension study was not blinded.

**Statistical Analyses**

All of the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 11.5 (SPSS Inc., Chicago, Illinois). The continuous variables were described using summary statistics, such as the means and standard deviations. The categorical variables were described using frequencies and percentages. The baseline characteristics of each group were compared using a t test for the continuous variables and the χ² test for the categorical variables.

We based power and sample size calculations on a 2-sided significance test at the .05 level, with 90 power and a dropout rate of 10%. This calculation yielded a sample size of 112 subjects to produce 102 who would complete 12-week treatment, which was exceeded in this study.

The main strategy involved repeated-measures analysis of variance (ANOVA). The primary outcome measure was the AIMS total score. For the dependent variables, 3 time points were used as the within effect, and group (EGb-761/placebo) was used as the between effect. If the group-by-time interaction effect was significant, then multivariate analysis of variance (MANOVA) was applied to examine the group difference at week 6 and the end of treatment (week 12). If the interaction was not significant, then no further statistical tests were performed. Analyses of changes in the PANSS score were performed in the same way.

Cognitive scores for the 2 groups were compared by using analysis of covariance with the cognitive scores at the end of treatment as the dependent variables and the baseline scores included as a covariate.

The change in the AIMS total score (week 12 vs baseline) with EGb-761 or placebo was calculated for each patient. For descriptive purposes, we also used independent-samples t tests to compare the mean reduction of the AIMS total score by the treatment group at 12 weeks. In secondary analysis, the proportions of patients having a response in each group were compared with the χ² test. We used multiple linear regression to investigate the potential response predictors associated with changes in the AIMS total scores. All of the statistical tests were 2-tailed and considered to be statistically significant if the P value was less than or equal to .05, and the Bonferroni-corrected P value was also reported for multiple linear regression.

**RESULTS**

**Demographic and Basic Descriptive Data**

The trial profile is shown in Figure 1. Overall, 171 participants entered the placebo lead-in period, 14 of whom were discontinued prior to random assignment (13 were classified as placebo responders, with AIMS total score reduction ≥25%, and 1 withdrew consent). The 157 patients who met the entry criteria were randomly assigned to the EGb-761 (n = 78) or placebo (n = 79) treatment groups. Of the 5 patients who withdrew from the study within the first 6 weeks, 1 was treated with EGb-761 and 4 received the placebo.

At baseline, there was no statistical difference between the 2 treatment groups in the demographic or clinical variables (Table 1).

The study results presented here are a summary of the intention-to-treat analysis for the 2 groups of randomly assigned patients, with last-observation-carried-forward imputation.

**Primary Outcomes**

On the basis of the AIMS total scores, EGb-761 was found to have a highly significant therapeutic effect during the treatment period. Repeated-measures MANOVAs on the total AIMS scores showed a significant group-by-time effect (F2,310 = 40.219, P < .0001), a significant group effect (F1,155 = 4.068, P = .045), and a significant time effect (F2,310 = 33.384, P < .0001). MANOVA showed that the total AIMS scores were significantly lower in the EGb-761 group than in the placebo group at weeks 6 and 12 (F = 22.705, P < .0001, effect size = 0.383, 95% CI, 0.425–1.562; and F = 84.182, P < .0001, effect size = 0.769; 95% CI, 1.332–2.528, respectively).
After 12-week treatment, TD changes were clinically significant in 11 patients, who showed no defined TD symptoms. Among them, the AIMS total scores of 4 patients dropped to 1 point (3 were receiving EGb-761 and 1 was receiving placebo), and the scores of 7 patients dropped to 2 points (all receiving EGb-761). There was a significant difference between the EGb-761 and placebo groups in the amount of improvement in TD (Table 2).

The mean difference in the change in these scores from baseline to 12 weeks between the 2 groups was 2.23 ± 0.28 (95% CI, 1.686–2.773).

To evaluate the treatment effect, we calculated the percentage of responders. At the end of treatment (week 12), improvement of 30% or more in the AIMS total score was noted in 40 (51.3%) of the 78 patients treated with EGb-761 and 4 (5.1%) of the 79 patients given the placebo (χ^2 = 41.56, P < .0001). The AIMS global score reflected the same changes (Table 2).

To determine whether concomitant administration of typical antipsychotics, atypical antipsychotics, or clozapine impacted treatment differentially, we included this medication factor in further analysis. The results showed that this medication factor did not significantly affect treatment outcome (data not shown).

After the treatment period, the EGb-761 group was followed up for 6 months and assessed with the AIMS at weeks 18, 24, and 36. There were no significant differences in the
AIMS total score among the different assessment points (1-way ANOVA, $F = 0.766, P = .514$).

**Secondary Outcomes**

**Psychopathologic symptoms.** Changes in the PANSS and its subscale scores are illustrated in Table 2. Significant improvement between baseline and follow-up occurred in both groups ($P < .05$). Repeated-measures MANOVAs on the PANSS total score showed a nonsignificant group-by-time effect ($F_{2,310} = 0.483, P = .617$, effect size = 0.055, power = 0.871), and there was no significant interaction between group and time for this score.

The PANSS positive and negative symptom-severity scores showed a similar profile, as did the total scores, with significant improvement between baseline and 12 weeks in both groups (both $P < .001$), but there were no significant interactions between group and time (both $P > .05$).

**Cognitive function and side effects.** Some of the patients could not complete the cognitive test due to noncooperation or serious mental deterioration. Thirteen subjects in the EGB-761 group and 25 subjects in the placebo group could not perform the CPT at baseline; all of the rest completed the test at both baseline and end of treatment. Ten subjects in the EGB-761 group and 15 subjects in the placebo group could not perform the Stroop test at baseline; all of the rest completed the test at both baseline and end of treatment. Among the patients who had completed the tests at both baseline and week 12, there were no between-group differences in the cognitive measures (CPT-37 and Stroop) from baseline to week 12 (Table 3).

Systemic side effects were evaluated by means of routine physical and neurologic examinations and laboratory tests and reviewed by applying the UKU Side Effect Rating Scale. These systemic side effects were all mild and brief. For none of the subjects were the routine blood cell count, chemistry, urinalysis, or electrocardiogram parameters significantly affected by the experimental treatment (data not shown).

One patient in the placebo group was withdrawn at week 4 because of intestinal obstruction. Three other patients in the placebo group and 1 in the EGB-761 group were withdrawn because of lost follow-up (hospital discharge). The patients who were withdrawn did not differ significantly from the other subjects in terms of their demographic or clinical characteristics. Overall, EGB-761 treatment at a dose of 240 mg/d was tolerated by the patients throughout the study, and no significant side effects were registered.

**Potential predictors of treatment response.** Multiple linear regression was performed to explore the predictors of response to EGB-761 treatment. The treatment effect was represented by the reduction in the AIMS total scores from baseline to week 12. Analyses were carried out in the EGB-761 group, which included 77 patients who completed the treatment. The covariates included a demographic variable (age) and clinical variables (psychopathology, antipsychotic dose, age at onset, age at first admission, duration of illness, baseline total AIMS score, presence or absence of current anticholinergic medication, presence or absence of current neuroleptic treatment, and smoking status). Because of the strong associations between age and duration of illness ($r = 0.93$) and age at onset and age at first admission ($r = 0.91$), and to avoid including completely collinear covariates in our multivariate analysis, we chose duration of illness and age at first admission for the regression analyses.

These analyses showed that the AIMS total score at baseline ($r = 0.603, P < .001, P < .001$ with Bonferroni correction) and age at first admission ($r = 0.223, P = .016, P = .128$ with Bonferroni correction) were positively associated with the reduction in the AIMS total score.

**DISCUSSION**

The results of this study suggest that EGB-761 (240 mg/d) is a safe and effective treatment for TD. Not only was a positive effect observed during treatment, but there was also a carryover effect for at least 6 months after the medication had been discontinued. To the best of our knowledge, this is the first study to demonstrate the clinically meaningful improvement of TD symptoms with EGB-761.

One possible explanation for the effects observed in this study is that they are due to the antioxidant and free radical–scavenging activities of EGB-761. TD is considered to be associated with long-term exposure to neuroleptic medications. It has been conjectured that neuroleptic drugs, by blocking dopamine receptors, may cause a secondary
increase in the turnover and metabolism of dopamine, which may lead to the increased formation of free radicals.

EGb-761 has been shown to be a potent antioxidant in vitro and in vivo. Numerous studies in animals and humans have demonstrated the protective effects of this extract against free radical–induced cell damage and dysfunction. It has also been reported to have an antioxidant effect and a positive effect on those illnesses in which an excess of free radical production may be involved, eg, cerebral insufficiency and mild and moderate dementia. The proposed mechanisms of action are (1) directly scavenging free radicals and (2) indirectly inhibiting the formation of free radicals. EGb-761 can scavenge reactive oxygen species such as OH, ROO, O2, NO, H2O2, and ferryl ion species. It can also enhance the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, catalase, and/or heme oxygenase-1, thereby indirectly contributing as an antioxidant. EGb-761 may also reduce the formation of free radicals by scavenging oxyradicals, thereby reducing oxidative stress and decreasing the chance of neurotoxicity. Hence, this extract may improve TD symptoms by reducing the concentration of free radicals. Such neuroprotective mechanisms may be relevant to the anti-TD effects of EGb-761.

Recent evidence suggests that TD may result from antipsychotic-induced damage to striatal cholinergic neurons. Many cholinergic drugs have been studied for the treatment of TD, although there is as yet no consensus result. EGb-761 has been observed to have a positive effect on cholinergic transmission, which may be an alternative mechanism for the clinical effects. However, it should be noted that there are many chemicals in the extract that could have many different CNS effects, which deserves further investigation.

Our study demonstrated that treatment was more effective in those patients who had worse symptoms (a higher AIMS score) at baseline, which corresponds to the results found by Shamir et al. Moreover, its efficacy was positively correlated with age at first admission for schizophrenia. To prevent the TD “masking” effect of atypical antipsychotics, our study was designed so that neuroleptic treatment was fixed throughout the double-blind period.

This study found no beneficial effects on PANSS ratings for EGb-761 at a dose of 240 mg/d, and no limitation was placed on the type of antipsychotic, in contrast to our previous study, which used an EGb-761 dose of 360 mg/d and fixed antipsychotic treatment with haloperidol. EGb-761 may improve cognitive function in Alzheimer’s disease patients with mild to moderate cognitive deficits, although the current findings showed no beneficial effect of the extract on cognitive function, as measured by the CPT-37 and Stroop test. This may be due to the limited tests of cognitive function we adopted, which may be insufficiently sensitive to detect subtle changes in such function. Moreover, the subjects recruited in this study were chronic cases, with a mean duration of illness of 23 years. These patients may have suffered from cognitive impairments that are too severe to be easily reversed by medication.

We also found that the therapeutic effect of EGb-761 was maintained after treatment was stopped. It should be noted that the improvement of symptoms was clearly temporally related to EGb-761 treatment, which may suggest that continuing treatment for a longer period of time may lead to greater clinical benefit. Thus, studies with longer follow-up periods are needed. However, since the follow-up was done in a nonblind fashion, these findings could be related to rater bias. The follow-up data would have been much stronger if the blind had been maintained and follow-up had been obtained on all subjects.

There are a number of limitations of our study. The main limitation is that the majority of patients received clozapine. In the guidance of clinical practice in China, when a patient displays TD, switching to clozapine is recommended. Furthermore, most of the patients in our present study were refractory to other drugs because they had been taking other antipsychotic drugs before switching to clozapine. Perhaps this could explain the lack of effect seen on the PANSS in our present study compared to the previous study using haloperidol. However, since no significant difference was noted in taking clozapine between EGb-761 and placebo groups, the effects of clozapine, if present, on TD in both groups were considered the same. The second major limitation in our present study is that data on the duration of TD had not been collected, which is an important factor that could have influenced the results of the treatment. According to the literature, TD that lasts more than 5 years is harder to treat. Hence, the further examination of the relationship between the duration of TD and clinical efficacy could be more fruitful. Third, we studied only male inpatients with schizophrenia; therefore, the current findings may be restricted to this sample. Fourth, the “placebo run-in” method moves the study a greater distance from how such a medication would be used clinically, thereby limiting, at least to some degree, the generalizability to clinical practice. Another limitation in our study was absence of systematic quantification of other movement disorders, such as parkinsonism or akathisia. Moreover, we adopted an EGb-761 dosage of 240 mg/d. It would be interesting to compare the efficacy of this dose with those of different dosages or other anti-TD agents.

In conclusion, the results of the present study demonstrate that EGb-761 treatment is beneficial for the treatment of antipsychotic-induced TD. There is as yet no consensus on a definitive treatment for TD. The potential usefulness of the extract in the treatment of TD has clinical importance, as it has only rare and transitory side effects in relatively high doses. Although our results are encouraging, these findings warrant further study and replication.

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

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