A Double-Blind, Placebo-Controlled Trial of Extract of *Ginkgo biloba* Added to Haloperidol in Treatment-Resistant Patients With Schizophrenia

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Background: Many studies have indicated that excess free radical formation may be involved in the pathogenesis of patients with schizophrenia. Some investigators suggested that the use of free radical scavengers might provide improvement in schizophrenia. The aim of this study was to determine the effectiveness and to evaluate the side effects of extract of *Ginkgo biloba* (EGb) plus haloperidol in chronic, treatment-resistant inpatients with schizophrenia.

Method: One hundred nine patients meeting DSM-III-R criteria for schizophrenia completed a double-blind, placebo-controlled, parallel-group study of EGb plus haloperidol. Fifty-six of the patients were randomly assigned to receive a fixed dose of 360 mg/day of EGb plus a stable dose of haloperidol, 0.25 mg/kg/day, and 53 were assigned to receive placebo plus the same dose of haloperidol for 12 weeks. Patients were assessed using the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), and the Scale for the Assessment of Positive Symptoms (SAPS) at baseline, week 6, and week 12 and the Treatment Emergent Symptom Scale (TESS) for side effects at week 12.

Results: There was a significant reduction in both groups in BPRS total score after 12 weeks of treatment ($p < .05$). However, a significant reduction in total SAPS and SANS scores was noted in the EGb group ($p < .05$), but not in the placebo group. There was a lower SAPS total score in the EGb group than in the placebo group at the end of 12 weeks of treatment ($p < .05$). Of those treated with EGb plus haloperidol, 57.1% were rated as responders as compared with only 37.7% of those receiving placebo plus haloperidol when assessed by the SAPS ($\chi^2 = 4.111$, $p = .043$). After 12 weeks of treatment, TESS subscore 1 (behavioral toxicity) and subscore 3 (symptoms of nerve system) were significantly decreased in the EGb group compared with the placebo group ($p < .05$).

Conclusion: EGb treatment may enhance the effectiveness of antipsychotic drugs and reduce their extrapyramidal side effects.

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The treatment of patients with schizophrenia, especially those with treatment-resistant and/or chronic illness course, is laborious. Although many antipsychotics have been developed and used widely in clinical practice, approximately 50% of patients with schizophrenia do not obtain adequate relief with conventional neuroleptics, with some 30% still exhibiting markedly disturbed behavior.[1] In addition, all the conventional neuroleptics cause extrapyramidal symptoms to a greater or lesser extent, which often leads to patient noncompliance with treatment. Therefore, the need to search for new treatment approaches for these treatment-refractory patients with schizophrenia remains.

Experimental and clinical data suggest that excess free radical formation may be involved in the pathogenesis of patients with schizophrenia[2–5]; for example, an increased superoxide dismutase (SOD) level[6,7] and an increase in lipid peroxides in patients' blood have been found in schizophrenia patients.[8–10] Therefore, some researchers have suggested that the use of free radical scavengers might provide improvement in schizophrenia.[3–5,11] Although radicals appear to be involved in the pathogenesis of schizophrenia, there have been very few studies of antioxidant treatment for the disease. Two studies[12,13] of vitamin C in schizophrenia produced conflicting results. Recently, Lohr[3] found a reduction in positive schizophrenic symptoms with vitamin E in a small sample.

Research in Germany and France has led to the production of a standardized extract of *Ginkgo biloba* (EGb),

which is obtained from the dried leaves of *Ginkgo biloba* trees according to a special manufacturing process.[14] Clinical studies indicated that chronically administered EGb is useful for those individuals who suffer from impairments in cognition and mood and associated symptoms, the origin of which could involve cerebrovascular insufficiency, neurodegeneration, or both.[15] One of the fundamental mechanisms involved in the therapeutic action of EGb is free radical scavenging.[16] However, no study to date has reported on the clinical effect of EGb on patients with schizophrenia. In light of the hypothesis that free radicals may be involved in the pathogenesis of schizophrenia, we postulate that EGb might be beneficial to chronic patients. Hence, the present study was performed to investigate the potential effects of EGb in patients with chronic, refractory schizophrenia in a 12-week double-blind, placebo-controlled setting.

METHOD

Subjects were recruited from the inpatient units of Beijing Huilongguan Hospital, a Beijing city–owned psychiatric hospital. All subjects satisfied the DSM-III-R criteria for schizophrenia (verified by the Structured Clinical Interview for DSM-III-R). The patients were considered resistant to treatment if they had no response to treatment with at least 2 antipsychotics for 3 months or longer at full dose, equivalent to chlorpromazine, 800 mg/day. Additional criteria included the following: duration of illness of at least 5 years, age between 18 and 60 years, and a Clinical Global Impressions scale[17] score of 4 or higher. Patients were excluded if they had any significant medical illness or were actively abusing alcohol or illegal drugs. Patients were also excluded if they had received vitamin C or vitamin E within 1 week before the start of the study or if they were pregnant or breastfeeding. Patients were also excluded if they displayed depressive symptoms as defined by a score of 25 or higher on the 18-item Hamilton Rating Scale for Depression.[18]

Study Design

Written informed consent was obtained from each patient before entry into the study. The trials consisted of a 1-week placebo lead-in followed by 12 weeks of double-blind treatment. A complete medical history and electrocardiogram were obtained, and a physical examination and laboratory tests were performed at study entrance. After a 1-week, single-blind, placebo lead-in, during which no psychotropic drugs were administered, patients who exhibited a 25% or greater reduction in Brief Psychiatric Rating Scale (BPRS)[19] total score were discontinued from the study.

Eligible patients were randomly assigned to either capsulized EGb (360 mg/day) or identically capsulized placebo in addition to the fixed dosage of haloperidol in a double-blind fashion. The patients reached the assigned dose of haloperidol, 0.25 mg/kg/day, by the end of the first week. A fixed titration to 360 mg (or 9 tablets) daily of EGb or placebo was administered with 3-times-daily dosing throughout the study. Both EGb and placebo were provided by the Honghui Pharmaceutical Company, Guilin, Guangxi Province, China. EGb contains mainly flavonal glycosides (24%) and the terpene substances ginkgolides and bilobalide (6%), which is in accordance with the criteria of the production of standardized EGb administered in Europe.[14] No concomitant psychotropic medications were permitted during the study, except chloral hydrate as needed for insomnia.

Clinical Ratings

BPRS, Scale for the Assessment of Negative Symptoms (SANS),[20] and Scale for the Assessment of Positive Symptoms (SAPS)[21] scores were assessed by 4 clinical psychiatrists who were blind to treatment condition. All patients were rated at baseline and after 6 and 12 weeks of treatment. The Treatment Emergent Symptom Scale (TESS)[22] was used by a psychiatrist to measure side effects in all patients after 12 weeks of treatment. To ensure consistency and reliability of ratings across the study, 4 psychiatrists who had worked at least 5 years in clinical practice simultaneously attended a training session in the use of the scales before the start of the study. The intraclass coefficients for the BPRS, SAPS, and SANS were 0.86, 0.96, 0.89, respectively (all p values < .05).

Statistical Analyses

The principal outcome analysis consisted of repeated-measures multivariate analyses of variance (MANOVAs) for the BPRS, SAPS, and SANS and their subscales, with a between-subject factor of drug (placebo vs. EGb) and a within-subject factor of time (week 1, week 6, and week 12). If the drug or drug-by-time interaction was significant, the interactive effect of gender was added as a between-subject factor in the repeated-measures MANOVA. If the drug or drug-by-time interaction effects were significant in the repeated-measures MANOVA, the effect of age, duration of illness, and baseline scores was tested by adding their variables to the analysis model as covariates.

Secondary analyses evaluated change during treatment with EGb or placebo and relationships between change scores and potential response predictors using analyses of variance and Pearson product moment correlations. Demographic characteristics of the EGb and placebo groups were compared by means of the Student 2-sample t test for continuous variables and the chi-square test or the Fisher exact test for categorical variables.

To quantify differences between the 2 groups, a patient was considered clinically responsive if there was a 30% decrease in the BPRS, SAPS, or SANS total scores, using a modification of the criteria of Kane.[1]

Table 1. Demographic and Clinical Data on Patients Entering the Double-Blind Period[a]

Characteristic	EGb (N = 56)	Placebo (N = 53)
Sex, N, M/F	33/23	30/23
Age, mean (SD), y	44.7 (7.7)	43.7 (8.2)
Duration of illness, mean (SD), y	21.7 (8.1)	21.2 (7.2)
Daily haloperidol dose, mean (SD), mg	16.8 (8.6)	16.5 (8.2)
Subtypes of schizophrenia, N		
Paranoid type	30	29
Disorganized type	12	10
Undifferentiated type	6	5
Residual type	8	9
CGI-S score, mean (SD)	5.9 (1.1)	6.0 (1.3)

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, EGb = extract of *Ginkgo biloba*.

RESULTS

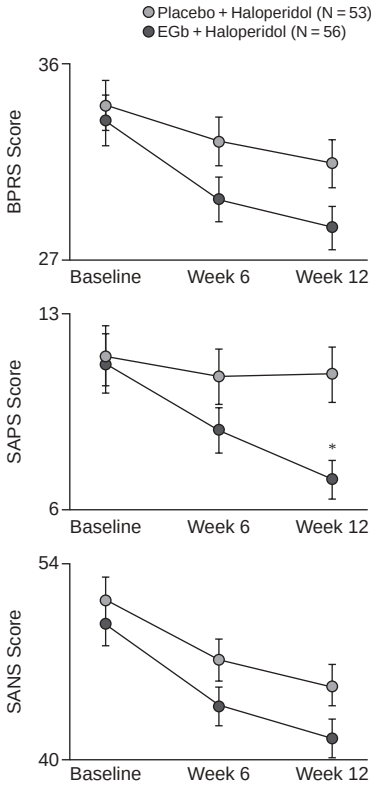
One hundred twelve patients entered the study, and 109 completed the 1-week placebo wash-in. They were randomly assigned to the placebo group (N = 53) or the EGb group (N = 56). Characteristics of the patient population at baseline are summarized in Table 1. The population was all Han Chinese, with a mean ± SD age of 44.2 ± 7.9 years (range, 27–61 years). No significant differences at baseline in any clinical variables were observed between the 2 groups (see Table 1). Of the 10 patients previously treated with haloperidol, 5 were assigned to the EGb group and the other 5, to the placebo group.

Clinical Response

Six subjects dropped out prior to week 6; 1 was receiving EGb, and 5 were receiving placebo (p = .11, Fisher exact test). One patient from the EGb group and 2 from the placebo group were dropped from the study owing to lack of efficacy. The other 3 withdrew from the placebo group, complaining of severe side effects. The patients who dropped out were considered nonresponders and were included in the comparison of clinical response between groups, but were not included in other analyses. Mean BPRS, SAPS, and SANS total scores across the 12-week study are displayed in Figure 1. Table 2 summarizes mean scores. All 3 psychiatric rating scales showed significant improvement in the EGb group between baseline and 12 weeks of treatment (BPRS, p = .001; SAPS, p = .004; SANS, p = .024). Improvement in the placebo group was significant only on the BPRS (p = .04); p values for improvement on the SAPS and SANS were .09 and .051, respectively.

At baseline, there was no statistically significant difference between the EGb and placebo groups in scores on the BPRS, SAPS, and SANS. At posttreatment, the EGb group showed a significantly lower SAPS score than the placebo group (F = 4.974, df = 1,101; p = .026; see Table 2).

Figure 1. Changes in Mean BPRS, SAPS, and SANS Scores Between Baseline and Week 12[a]



[a]The EGb group showed significant improvement between baseline and 12-week treatment on the BPRS (p = .001), SAPS (p = .004), and SANS (p = .024). The placebo group had significant improvement only on the BPRS (p = .04). A significant difference in SAPS score at the end of 12-week treatment was observed between the EGb and placebo group. Abbreviations: BPRS = Brief Psychiatric Rating Scale, EGb = extract of *Ginkgo biloba*, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
*p = .026.

Repeated-measures MANOVAs on the SAPS total score showed a significant drug effect (F = 5.253, df = 2,101; p = .024), a significant time effect (F = 6.15, df = 2,202; p = .005), and a nonsignificant drug-by-time effect (F = 0.464, df = 2,202; p = .63). We wondered whether gender contributed to the overall variance. Therefore, additional repeated-measures MANOVAs were performed with both group and gender as main effects, as well as the group-by-gender interaction. There was still a significant drug effect (F = 6.233, df = 1,99; p = .014), as well as a significant sex effect (F = 6.157, df = 1,99; p = .015) and a nonsignificant drug-by-sex effect (F = 0.35, df = 1,99; p = .58). When the effect of age and illness course was examined by adding them to the repeated-measures MANOVAs as covariates, a significant drug effect with age (F = 6.604, df = 1,100; p = .012) and a significant drug effect with illness course (F = 5.466, df = 1,100; p = .021) together with a significant drug ef-

Table 2. Comparison of Mean Scores at Baseline, Week 6, and Week 12 on Psychiatric Rating Scales in the EGb Group and the Placebo Group[a]

	EGb (N = 56)			Placebo (N = 53)		
Measure	Baseline	Week 6	Week 12	Baseline	Week 6	Week 12
BPRS	33.9 (11.2)	30.0 (9.6)*	28.7 (7.2)†	34.3 (11.4)	32.6 (10.3)	31.6 (8.7)*
SAPS	11.4 (11.7)	8.9 (10.6)	7.1 (8.4)†	11.7 (13.2)	10.9 (11.8)	11.0 (10.5)‡
SANS	49.4 (15.3)	44.3 (15.4)	42.3 (15.6)*	50.9 (13.7)	47.2 (13.7)	45.6 (14.1)

[a]All values reported as mean (SD). Abbreviations: BPRS = Brief Psychiatric Rating Scale, EGb = extract of *Ginkgo biloba*, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
*p < .05, pretreatment vs. posttreatment.
†p < .01, pretreatment vs. posttreatment.
‡p < .05, EGb group vs. placebo group.

Table 3. Clinical Effectiveness of Treatment Based on Psychiatric Rating Scales[a]

Measure	Responders (N)	Nonresponders (N)	df	χ^2	p
BPRS					
EGb	33	23	1	1.512	.219
Placebo	25	28			
SAPS					
EGb	32	24	1	4.111	.043
Placebo	20	33			
SANS					
EGb	22	34	1	0.992	.319
Placebo	16	37			

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, EGb = extract of *Ginkgo biloba*, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

fect with both course and age ($F = 5.363$, $df = 1,99$; $p = .023$) was still observed. When the SANS total score was added as a covariate, there was still a significant drug effect ($F = 4.936$, $df = 1,100$; $p = .029$) and a significant drug-by-SANS-total-score effect ($F = 3.491$, $df = 2,200$; $p = .032$). In addition, repeated-measures MANOVAs on the BPRS and SANS total scores revealed a trend toward significance in the drug effect (BPRS: $F = 3.667$, $df = 1,101$; $p = .058$; SANS: $F = 2.966$, $df = 1,101$; $p = .08$) and a significant time effect (BPRS: $F = 10.11$, $df = 2,202$; $p = .000$; SANS: $F = 14.37$, $df = 2,202$; $p = .000$).

Results of clinical ratings of response and nonresponse on the BPRS, SAPS, and SANS are shown in Table 3. The percentage of patients who received EGb and who were rated as responders on the SAPS was significantly higher than the percentage of patients who received placebo who were rated as responders ($\chi^2 = 4.111$, $df = 1$, $p = .043$).

Adverse Effects

The total TESS score represents the severity of side effects, and 6 subscores represent the adverse events in different systems of the body. There was no distinguishable difference in mean total scores between the EGb group (1.8 ± 2.8) and the placebo group (2.7 ± 4.6) ($F = 2.57$, $df = 96$, $p = .07$). When subscores were analyzed further, it was found that TESS subscore 1 (behavioral toxicity) and subscore 3 (symptoms of the nerve system) were significantly lower in the EGb group than in the placebo group, with mean scores of 0.24 ± 0.21 versus 0.96 ± 0.92 ($F = 2.96$, $df = 96$, $p = .03$) on subscore 1 and 0.37 ± 0.32 versus 1.06 ± 0.94 ($F = 3.12$, $df = 96$, $p = .02$) on subscore 3.

DISCUSSION

To our knowledge, this is the first double-blind, randomized, large-sample clinical trial studying treatment with EGb plus an antipsychotic drug for schizophrenia. The results of our study suggest that EGb treatment may enhance the effectiveness of antipsychotic drugs for treatment-resistant schizophrenia, especially for positive symptoms, and reduce the extrapyramidal side effects of antipsychotics.

In the present study, a dose of 360 mg/day of EGb plus haloperidol was found to be clinically superior to placebo plus haloperidol in the treatment of inpatients with chronic schizophrenia. It should be mentioned, however, that the mean reduction on all rating scales was comparatively low in both groups due to the chronic, treatment-resistant nature of the patients' illness. There was some symptomatic improvement in the haloperidol-plus-placebo–treated group, mainly shown on the BPRS, but significant improvement in BPRS, SAPS, and SANS scores was noted in the haloperidol-plus-EGb–treated group. These results show that EGb plus haloperidol was therapeutically more effective in the treatment of both positive symptoms and negative symptoms than haloperidol alone. It is worth noting that EGb treatment produced better effectiveness than haloperidol alone for negative symptoms, because it is well known that few therapies have been available for the treatment of negative symptoms of schizophrenia. The reduction of negative symptoms in patients treated with EGb reported in our study may be at least partially related to the cognition-activating effects of EGb, since studies indicate that EGb may act by increasing "drive," i.e., by increasing alertness or awareness.[23] However, cognitive efficacy was not assessed using a test of mental ability in this trial. No firm conclusion can be drawn at this time regarding the contributions of EGb on cognitive function in chronic schizophrenia. Further studies are necessary to determine the extent to which EGb may fill the pressing need for cognitive activators with undisputed efficacy for schizophrenia.

The main finding of the present study is that EGb combined with haloperidol was more effective than placebo combined with haloperidol in the treatment of positive symptoms of schizophrenia. The results showed that the mean SAPS score was significantly lower in the EGb group than in the placebo group at posttreatment. The

main finding was confirmed by the response rate measures based on SAPS score, which showed that the percentage of EGb-treated patients who were rated as responders was significantly higher than the corresponding percentage in the placebo group. Furthermore, repeated-measures MANOVAs on the SAPS total score showed a significant drug effect that also supported the main finding. In addition to significant improvement in symptoms, it is noteworthy that EGb may reduce the side effects produced by haloperidol. The main reduction of side effects was shown in the TESS behavioral toxicity factor and the nerve system symptom factor, suggesting that EGb could reduce extrapyramidal side effects. Research has revealed that the effectiveness of conventional neuroleptics is commonly associated with their side effects; that is, the greater the effectiveness of the medications, the more likely adverse effects will occur. It is postulated that blockade of mesolimbic D_2 receptors may have predominantly antipsychotic action and that concomitant blockade of these receptors in the basal ganglia may cause extrapyramidal symptoms to develop.[24,25] Our findings showed that EGb could either enhance the efficacy of antipsychotic medication or alleviate its side effects, suggesting that the pharmacologic profile of EGb might be different from those of the conventional neuroleptics.

Some studies have indicated that abnormal oxyradical metabolism in the central nervous system (CNS) may be secondary to increased levels of dopamine, because dopamine can auto-oxidize to form radicals or contribute to radical formation through metabolism by the enzyme monoamine oxidase, which forms hydrogen peroxide.[2,26] The brain is a highly oxygenated structure, receiving one fifth of the body's total cardiac output, and is therefore particularly susceptible to free radical formation and attack.[2,3] Free radicals can initiate lipid peroxidation, resulting in altered membrane structure and function and causing mental symptoms. On the other hand, free radicals may contribute to neuronal damage, particularly to dopamine neuronal damage, and lead to degenerative pathology,[27] which may be associated with negative symptoms. Hence, free radicals might have a role in the pathologic process of schizophrenia.

One of the most important aspects of the pharmacologic profile of EGb is its significant free radical–scavenging activity and reduction of oxidative stress.[28,29] In scavenging oxyradicals, EGb may attenuate the damaging effects of excess radicals caused by the possible hyperdopaminergic activity. Therefore, EGb in combination with a neuroleptic could ameliorate the symptoms of schizophrenia. Furthermore, for a complex product like EGb, a whole spectrum of substances appear to be responsible for its polyvalent therapeutic action against the pathologic process. The clinical beneficial effects of EGb may be due to the combination of its various protective, curative, and modulating properties. In vitro studies with EGb exhibited a range of activities that included radical scavenging, antagonism to platelet-activating factor, blood vessel relaxation, enzyme inhibition, and modification of energy metabolism, particularly in conditions of hypoxia.[29] In this way, EGb may improve physiologic function and balance cell homeostasis by its polyvalent therapeutic action with a broad spectrum of substances and consequently could enhance the effectiveness of haloperidol.

The finding that EGb plus haloperidol treatment produced greater efficacy for positive symptoms is consistent with the hypothesis that positive symptoms are related to hyperdopaminergic activity, as well as to increased free radicals. In our previous research,[30,31] we found that mean blood SOD concentration was significantly higher in schizophrenic patients than in control subjects. After patients were divided into subgroups according to whether they had higher or lower mean BPRS, SAPS, and SANS scores, blood SOD levels were significantly elevated in patients with higher total BPRS or SAPS scores in comparison to those with lower total scores, but no significant differences were found between higher and lower SANS score subgroups. Also, there was significant positive correlation between SOD levels and total BPRS and SAPS scores. These results suggest that free radicals could have a link to the positive symptoms of schizophrenia.[30,31] The beneficial effect of EGb on positive symptoms is attributed to their ability to scavenge free radicals produced by hyperdopaminergic activity. Therefore, greater efficacy for positive symptoms shown in EGb plus haloperidol treatment indicated a correlation between positive symptoms and free radicals.

The TESS results showed that the behavioral toxicity subscores and nerve system symptom subscores were significantly lower in the EGb group than in the placebo group at posttreatment. This suggests that EGb might have reduced liability for extrapyramidal symptoms. It has been conjectured that neuroleptic treatment may increase free radical production. By blocking dopamine receptors, neuroleptics cause a secondary increase in the turnover and metabolism of dopamine, which may lead to increased formation of dopamine quinones and hydrogen peroxide.[2,3] In this way, neuroleptics might contribute to neuronal damage, i.e., to persistent tardive dyskinesia.[32] When EGb is added to haloperidol, it may capture the excess free radicals, reduce ongoing damage, and increase the self-renovation of neuron. In addition to alleviating neuronal damage by free radical scavenging, EGb could also increase energy metabolism and inhibit neurotransmitter-degrading enzymes. This effect could be related to improved cerebral circulation and/or to a direct protective effect of EGb on neural tissue. In this way, EGb could ameliorate the side effects of haloperidol.

Limitations of the present study include the relatively limited sample size and the relatively short duration of the trial. In addition, a limitation of the design is the use of

haloperidol as the antipsychotic treatment at a time when newer-generation antipsychotic drugs are the standard of care. Therefore, more clinical trials with larger samples of patients and longer duration of treatment with EGb are needed to determine any long-term risks and benefits before a final conclusion can be made regarding the use of EGb in schizophrenia patients. In addition, a further study is warranted to investigate whether EGb shows similar benefits in augmenting the new antipsychotics, which already have the capacity to improve positive and negative symptoms and have better profiles in terms of extrapyramidal side effects.

In summary, EGb appeared to increase the effectiveness and reduce the side effects of neuroleptic medication. The mechanism of its action may involve mainly scavenging of free radicals, improving physiologic function, and balancing cell homeostasis. In the CNS, it could alleviate the damage secondary to hyperdopaminergic activity, relieve the harmful factors to neurons, and enhance the self-repair of neurons. For these reasons, EGb in combination with neuroleptic treatment might better ameliorate the symptoms of schizophrenia than neuroleptic treatment alone. The finding of effectiveness with EGb in combination with haloperidol lends support to the hypothesis that higher production of free radicals may be involved in the pathogenesis of schizophrenia, and antioxidant action and free radical scavenging may be helpful in alleviating some of the symptoms of schizophrenia.

Drug names: chlorpromazine (Thorazine and others), haloperidol (Haldol and others).

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