

Does the addition of lamotrigine to risperidone improve psychotic symptoms and cognitive impairments in chronic schizophrenia?

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Background: Cognitive deficits are central features of schizophrenia, and cognitive dysfunction has been identified as a major determinant of long-term outcome and quality of life. It has been reported that lamotrigine, a mood stabilizer that inhibits glutamate release, can augment clozapine treatment in patients with chronic refractory schizophrenia. In addition, lamotrigine, unlike most antipsychotic drugs, can reverse psychotomimetic symptoms induced by ketamine and it may improve some aspects of cognitive dysfunction associated with schizophrenia such as attention, learning and memory. **Objective:** The objective of the study was to assess the efficacy of lamotrigine as an adjuvant agent in the treatment of patients with chronic schizophrenia and, in particular, its effect on cognitive performance (attention) in an 8-week, double-blind placebo-controlled trial. **Method:** A total of 36 inpatients in the active phase of schizophrenia who met the Diagnostic and Statistical Manual for Mental Disorders IV criteria for the chronic stage of the illness were chosen as eligible participants in the study. Patients were allocated in a random fashion, 18 to risperidone 6 mg/day plus lamotrigine 150 mg/day and 18 to risperidone 6 mg/day plus placebo. **Results:** Although both protocols significantly decreased the score of the positive, negative and general psychopathologic symptoms over the trial period, the combination of risperidone and lamotrigine demonstrated a significant superiority over risperidone alone in the treatment of negative symptoms, general psychopathology symptoms as well as Positive and Negative Syndrome Scale total scores. In addition, patients' attention improved significantly in the lamotrigine group on the Stroop color-naming subtest (time and error). There were no significant differences between the two groups in terms of extrapyramidal symptoms and observed side effects. **Conclusions:** The study indicates that lamotrigine is a potential adjunctive treatment strategy for chronic schizophrenia and it may improve the attention domain of cognition impairment associated with the illness.

Traditionally, schizophrenia was considered to be a severe psychiatric disorder, with a chronic course and an unfavorable outcome [1]. The discovery of antipsychotics in the 1950s revolutionized the treatment of the disease and led the focus to the positive symptoms. However, by the 1960s it had become obvious that the reduction in positive symptoms did not lead to a recovery from schizophrenia and did not significantly improve the functional outcome [2]. Indeed, schizophrenia is considered to be the most expensive psychiatric disorder to treat, due to its cognition impairments. Cognitive deficit is the core and enduring feature of the illness and is more important than the positive and, to some extent, the negative symptoms in predicting the functional outcome [3].

Research has consistently demonstrated that patients with schizophrenia suffer from cognition impairments as well as positive and negative

symptoms. Specific deficits have been identified in the areas of attention, memory and executive function [4]. For years the focus of treatment for schizophrenia has been on the psychotic symptoms, partly because this approach has been successful. Unfortunately, however, the effective treatment of psychotic symptoms in schizophrenia does not reduce cognitive impairment, which causes disability and indirectly contributes to the cost of the illness [4].

Emerging evidence has suggested that patients taking novel antipsychotics may perform better on cognitive testing than those on traditional antipsychotics [5,6]. There are only a few studies examining the efficacy of mood stabilizers or atypical antipsychotics for cognitive function in schizophrenia [6]. The Stroop color word test (SCWT) is a cognitive test often used for the study of selective attention. It has been shown that schizophrenia patients do not perform as

Keywords: attention, chronic schizophrenia, cognition, lamotrigine, risperidone

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well as healthy controls on the SCWT [7]. This has been attributed either to a deficit of inhibitory processes underlying selective attention or to a working memory deficit due to prefrontal dysfunction [8].

The schizophrenia-like symptoms of phenylcyclidine are attributed to the activity of the drug at the *N*-methyl-D-aspartate (NMDA) receptor [9]. It has been reported that lamotrigine, a mood stabilizer that inhibits glutamate release, can augment clozapine treatment in patients with chronic refractory schizophrenia [10–12]. In addition, lamotrigine, unlike most antipsychotic drugs, can reverse psychotomimetic symptoms induced by ketamine and it may improve some aspects of cognitive dysfunction associated with schizophrenia such as attention, learning and memory [9,13].

The objective of the current study was to assess the efficacy of lamotrigine as an adjuvant agent in the treatment of patients with chronic schizophrenia, and in particular, its effect on cognitive performance (attention), in an 8-week, double-blind, placebo-controlled trial.

Methods

Trial organization

This was an 8-week, parallel-group, placebo-controlled trial undertaken in the Roozbeh Psychiatric Hospital in Tehran, Iran between October 2003 and January 2005.

Participants

Eligible participants in the study were 36 patients with schizophrenia. All participants were inpatients in the active phase of illness and met Diagnostic and Statistical Manual for Mental Disorders DSM-IV criteria for chronic schizophrenia [14]. The minimum score of 60 on the Positive And Negative Syndrome Scale (PANSS) [15] was required for entry into the study. The PANSS includes 30 items on three subscales, seven items covering positive symptoms, seven covering negative symptoms and 16 covering general psychopathology. In addition, a total score presents all three parts. The patients did not receive neuroleptics from a period of 1 week prior to entering the trial or a depot neuroleptic for at least 2 months prior to the study. Patients were excluded if they had a clinically significant organic, neurologic disorder, current abuse or dependence on drugs within 6 months, mental retardation (intelligence quota <70), history of renal or liver function

impairments, history of allergic reaction to lamotrigine and participation in an investigational drug trial within 30 days before the start of the trial. Women were excluded from the trial if they were pregnant or lactating. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions, and has approved by the ethics committee at Tehran University of Medical Sciences (Tehran, Iran). Written informed consents were obtained before entering into the study.

Intervention

Patients were randomly allocated as:

- 18 to risperidone 6 mg/day plus lamotrigine 150 mg/day (50 mg in the first week and titrated up to 150 mg/day at week 6)
- 18 to risperidone 6 mg/day plus placebo for an 8-week, double-blind, placebo-controlled study

One patient from each group dropped out of the study leaving a total of 34 patients who met the DSM-IV criteria for schizophrenia to complete the trial. Patients also received biperiden if they had experienced extrapyramidal symptoms. Patients were assessed by a third-year resident of psychiatry at baseline and 2, 4, 6 and 8 weeks after starting the medication.

Outcome

The principal measure of outcome was the PANSS. The rater used standardized instructions in the use of PANSS. The mean decrease in PANSS score from baseline was used as the main outcome measure of response of schizophrenia to treatment. Extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) [16]. Patients were randomized to receive lamotrigine or placebo in a 1:1 ratio using a computer-generated code. Throughout the study, the medication administrator, the rater and the patients were blind to assignments.

Stroop color word test

The test was performed in a standardized fashion in a single session of about 20 mins by ZM Alem who was blind to treatments [17]. Patients were tested individually in a sound-free room, similar to that described by Abramczyk and colleagues [7]. Patients sat at a distance where the words could easily be read and were asked to maintain visual scanning of the lists, switching from item to item and column to column.

Subtests

Reading of black printed words (Cards 1) and naming colors of printed words with non-matching colors and words (Cards 2), was carried out according to the procedure described by Liddle and Moris [8]. A short practice period preceded the testing for each card to ensure that participants understood the instructions and were performing the task appropriately. Error criteria included:

- Card 1: breaking the sequence of words or trying to correct him or herself
- Card 2: reading color, or trying to correct him or herself

Each card consisted of 100 stimuli distributed in 20 lines and 5 columns.

Safety measures

Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on days 3, 7, 14, 28, 42 and 56. Laboratory tests obtained included a complete blood cell count with differential, liver- and renal-function tests.

Statistical analysis

A two-way repeated measures analysis of variance (time–treatment interaction) was used. The two groups as a between-subjects factor (group) and the five measurements during treatment as the within-subjects factor (time) were considered. This was carried out for positive, negative, general psychopathology subscale and PANSS total scores. A Greenhouse–Geisser correction was used for sphericity. In addition, a one-way repeated measures analysis of variance with a two-tailed *post hoc* Tukey mean comparison test were performed in the change from baseline in each

group. The Tukey test is a popular *post hoc* test that compares pairs of group means. To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student's *t*-test with a two-sided *p*-value was used. To compare the demographic data and frequency of extrapyramidal side effects between the protocols, Fisher's exact test was carried out. Results are presented as mean \pm standard error of the mean (SEM). Differences were considered significant with $p < 0.05$. To consider, $\alpha = 0.05$, $\beta = 0.2$, the final difference between the two groups, a score of at least 5 on the PANSS rating scale, $S = 5$ and power = 0.8, the sample size was calculated as at least 15 in each group. In addition, an intention-to-treat (ITT) analysis with last observation carried forward (LOCF) procedure was carried out.

Results

A total of 58 patients were screened for the study and 36 were randomized to trial medication (18 patients in each group). No significant differences were identified between patients randomly assigned to the group 1 or 2 condition regarding basic demographic data including age, gender, number of hospitalization, years of schooling and mean duration of illness (Table 1). One patient from each group dropped out during the trial due to withdrawal of consent.

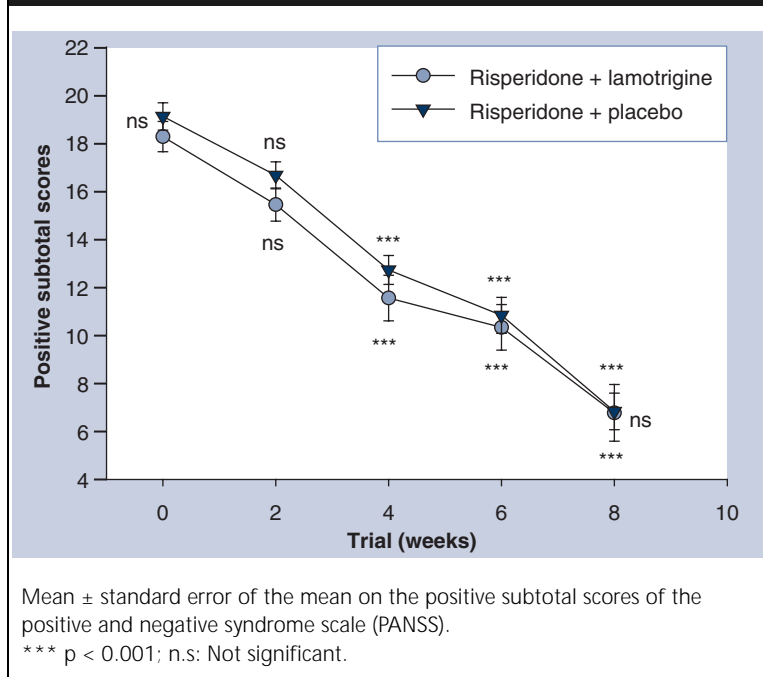
Positive symptoms

The mean \pm SEM scores of two groups of patients are shown in Figure 1. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.97$; *d.f.* = 34; $p = 0.33$). The difference between the two protocols was not significant as indicated by the effect of the group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 0.84$; *d.f.* = 1; $p = 0.36$). The behavior of the two treatment groups was homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 0.32$; *d.f.* = 2.33; $p = 0.75$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the positive subscale scores of PANSS rating scale ($p < 0.0001$). In both groups, *post hoc* comparisons showed a significant change from week 4 compared with their baselines. The difference between the two protocols was not significant at the 8-week endpoint ($t = 0.03$; *d.f.* = 34; $p = 0.96$).

Table 1. Baseline data.

	Risperidone + lamotrigine	Risperidone + placebo	<i>p</i>
Age (mean \pm standard deviation)	30.16 \pm 7.47	30.88 \pm 8.35	0.78
Gender	Male: 10; Female: 8	Male: 9; Female: 9	1.00
Schooling (year)	9.00 \pm 3.10	9.38 \pm 3.27	0.71
Months of illness (mean \pm standard deviation)	94.11 \pm 73.32	102.11 \pm 63.37	0.72
Number of hospitalizations (mean \pm standard deviation)	4.11 \pm 1.81	4.38 \pm 2.03	0.66

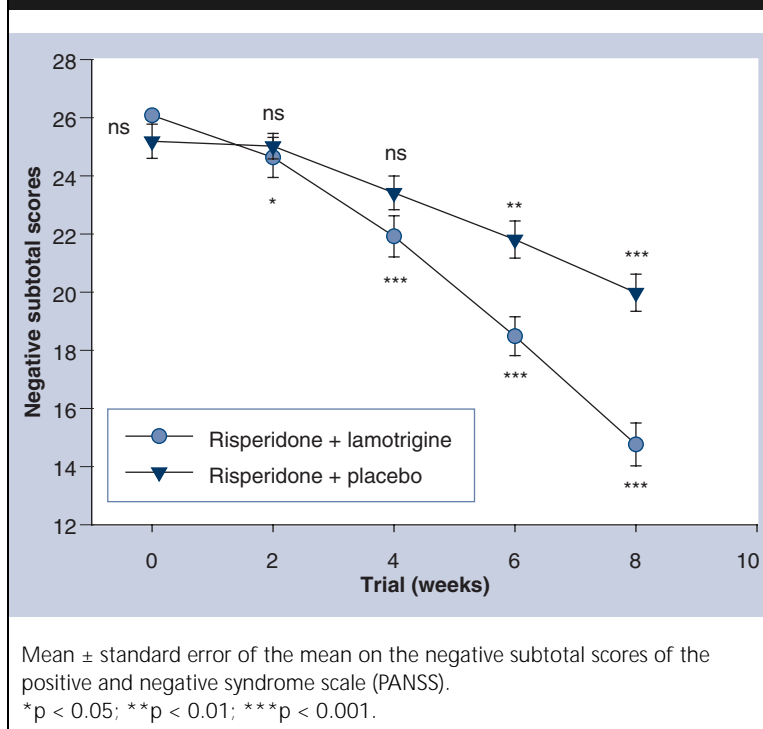
Figure 1. Risperidone plus lamotrigine versus risperidone plus placebo.



Negative symptoms

The mean ± SEM scores of two groups of patients are shown in Figure 2. There were no significant differences between the two groups

Figure 2. Risperidone plus lamotrigine versus risperidone plus placebo.



at week 0 (baseline) on the PANSS ($t = 0.91$; $d.f. = 34$; $p = 0.36$). The difference between the two protocols was significant, as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 0.23$; $d.f. = 1$; $p = 0.01$). The behavior of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 17.97$; $d.f. = 1.72$; $p = 0.0001$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the negative subscale scores of PANSS rating scale ($p < 0.0001$). In the lamotrigine group, *post hoc* comparisons showed a significant change from week 2 and in the placebo group from week 6 compared with their baselines. The difference between the two protocols was significant at the end point (week 8) ($t = 5.31$; $d.f. = 34$; $p = 0.0001$).

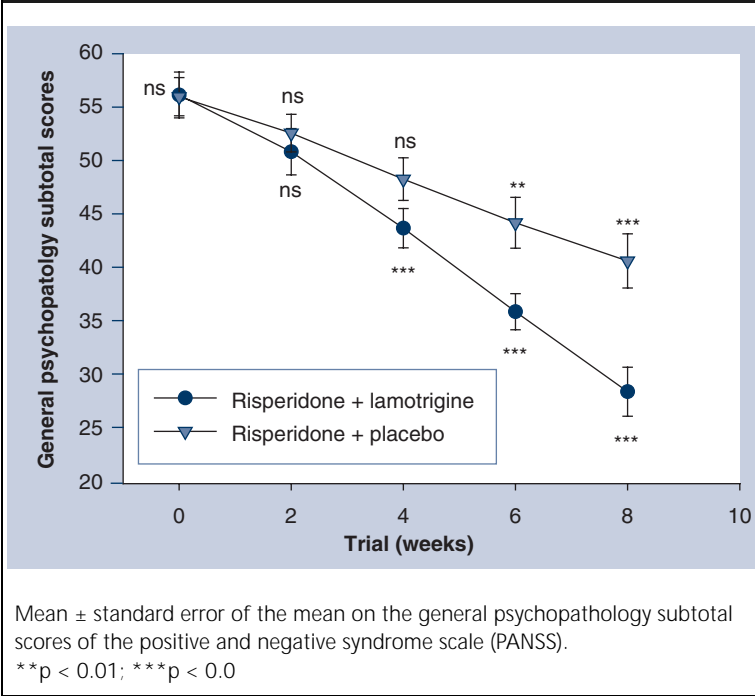
General psychopathologic symptoms

The mean ± SEM scores of two groups of patients are shown in Figure 3. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.05$; $d.f. = 34$; $p = 0.95$). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 4.18$; $d.f. = 1$; $p = 0.04$). The behavior of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 10.86$; $d.f. = 1.40$; $p = 0.001$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the general psychopathologic symptoms subscale scores of PANSS rating scale ($p < 0.0001$). In the lamotrigine group *post hoc* comparisons showed a significant change from week 4 and in the placebo group from week 6 compared with their baselines. The difference between the two protocols was significant at the 8-week endpoint ($t = 5.31$; $d.f. = 34$; $p = 0.0001$).

Positive & negative syndrome scale total scores

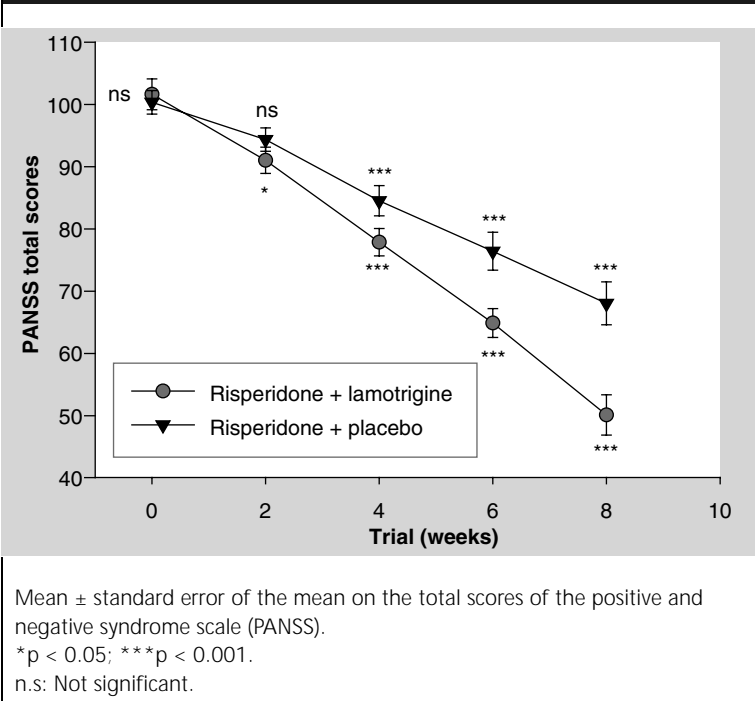
The mean ± SEM scores of two groups are shown in Figure 4. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.40$; $d.f. = 34$; $p = 0.68$). The difference between the two protocols was significant, as indicated by the effect of group, the between-subjects factor

Figure 3. Risperidone plus lamotrigine versus risperidone plus placebo.



(Greenhouse–Geisser corrected: $F = 6.71$; $d.f. = 1$; $p = 0.01$). The behavior of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse–Geisser

Figure 4. Risperidone plus lamotrigine versus risperidone plus placebo.



corrected: $F = 9.80$; $d.f. = 1.72$; $p = 0.0001$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols on the total scores of PANSS rating scale ($p < 0.0001$). In the lamotrigine group *post hoc* comparisons showed a significant change from week 2 and in the placebo group from week 4, compared with their baselines. The difference between the two protocols was significant at the endpoint (week 8) ($t = 3.77$; $d.f. = 34$; $p = 0.0006$).

Neuropsychological test

Stroop color word test scores

A summary of neuropsychological scores and statistical analysis is presented in Table 2. There were no significant differences between the two groups at week 0 (baseline) on the Stroop word reading and Stroop color naming (time and error). The difference between the two protocols was significant at the endpoint (week 8) only on the Stroop color-naming score (time and error) ($p = 0.02$ and 0.001 , respectively). A significant difference at the end point compared with the baseline was observed only in the lamotrigine group. This significant difference was observed on the Stroop color-naming score.

Extrapyramidal symptoms rating scale

Although the means ESRS for the placebo group were higher than for the lamotrigine group, the differences were not significant over the trial (Table 3). No significant difference was observed between the overall mean biperiden dosages in two groups. (100.33 ± 81.38 and 137.66 ± 87.00 for lamotrigine and placebo group, respectively; mean ± standard deviation; $p = 0.19$).

Clinical complications & side effects

Ten side effects were observed over the trial. The difference between lamotrigine and placebo in the frequency of side effects was not significant (Table 4).

Discussion

The main domains of cognition that are disrupted in schizophrenia include attention, executive function, and learning and memory [18]. Although conventional antipsychotics are effective in treating positive symptoms, they lack the ability to improve either negative symptoms or cognitive impairments. Several lines of evidence have demonstrated superior efficacy of atypical antipsychotics on cognitive impairments in schizophrenia compared with

Table 2. Stroop Word-Reading and Stroop Color-Naming tests at baseline and endpoint.

	Week 0		p	Week 8		p	Week 0 vs. Week 8	
	Risperidone + lamotrigine (mean ± standard deviation)	Risperidone + placebo (mean ± standard deviation)		Risperidone+ lamotrigine (mean ± standard deviation)	Risperidone + placebo (mean ± standard deviation)		Lamotrigine (p-value)	Placebo (p-value)
Stroop word reading (time)	112.66 ± 17.47	111.77 ± 19.89	0.88	111.27 ± 16.20	110.66 ± 18.68	0.91	0.80	0.86
Stroop color naming (time)	304.22 ± 47.26	306.77 ± 46.80	0.87	266.16 ± 39.83	295.61 ± 34.15	0.02	0.01	0.41
Stroop word reading (error)	8.55 ± 3.80	8.83 ± 3.56	0.82	8.05 ± 3.43	8.38 ± 3.07	0.76	0.68	0.69
Stroop color naming (error)	34.72 ± 11.44	36.94 ± 12.25	0.57	25.55 ± 6.05	33.83 ± 7.83	0.001	0.005	0.37

older drugs [5,6]. Although atypical antipsychotics have some benefit on cognitive function, further effort to improve cognitive function are still needed.

This study showed that the addition of 150 mg lamotrigine to antipsychotic medication provided a better outcome compared with the group who received an antipsychotic alone. The clinical improvement was significantly greater in the adjunctive 150-mg lamotrigine group with respect to negative symptoms, general psychopathologic symptoms and PANSS total scores over 8 weeks' trial. No significant differences were observed between the means of the two groups on the positive scores. Although the mean ESRS for the placebo group were higher than for the lamotrigine group, the differences were not significant over the trial. Clinical characteristics

of the patients, such as sex, age and duration of illness, years of schooling and the number of hospitalizations did not differ between groups and cannot explain differences in the therapeutic outcome.

In addition, this trial tested the hypothesis that lamotrigine, a drug reported to inhibit glutamate release, will improve the attention domain of cognition in patients who received risperidone. The present study is, to our knowledge, the first randomized, double blind and placebo controlled trial that indicates that patients receiving risperidone plus lamotrigine 150 mg/day perform better on tests assessing attention compared with patients receiving risperidone alone. Our findings of improvement in attention with lamotrigine are in line with a number of animal and clinical studies that have indicated that lamotrigine can attenuate

Table 3. Extrapyramidal symptoms based on extrapyramidal symptoms rating scale.

	Risperidone + lamotrigine (mean ± standard deviation)	Risperidone + placebo (mean ± standard deviation)	p
Day 0	2.00 ± 4.33	2.12 ± 4.58	0.93
Day 7	7.75 ± 8.50	8.68 ± 8.51	0.75
Day 14	11.68 ± 11.48	13.87 ± 11.96	0.60
Day 28	6.81 ± 4.69	9.68 ± 6.99	0.18
Day 42	4.43 ± 4.70	5.00 ± 4.38	0.72
Day 56	2.93 ± 2.99	3.25 ± 3.27	0.78

Table 4. Number of patients with side effects.

Side effects	Risperidone + lamotrigine	Risperidone + placebo	p
Rash	2	1	1.00
Ataxia	2	0	0.48
Itching	4	1	0.33
Diarrhea	4	1	0.33
Dizziness	3	1	0.60
Blurred vision	2	1	1.00
Nausea	5	1	0.17
Headache	11	9	0.79
Vomiting	3	0	0.22
Hair loss	1	0	1.00

or reverse the neuropsychiatric effects of ketamine both in rats and humans [9,10]. Moreover, it is in agreement with the studies that indicate lamotrigine adjuvant treatment may improve psychotic symptoms when it is added to both conventional and atypical antipsychotics [19,20].

These results are likely to have important implications for community outcome with schizophrenia. No severe dermatologic side effects were observed with lamotrigine and none of the side effects were considered disturbing by the patients who receive lamotrigine compared with risperidone alone

There are several limitations for the current study. First, other domains of cognition such as executive function and verbal memory were not assessed in this trial. The dose of risperidone

and lamotrigine were fixed throughout the trial so it is not possible to present optimal pharmacologic treatment.

Expert opinion

The present study indicates lamotrigine as a potential adjunctive treatment strategy for chronic schizophrenia and may improve attention domain of cognition impairment associated with schizophrenia. Therefore, glutamate release inhibiting drugs such as lamotrigine can reduce the hyperglutamegic consequence of NMDA receptor dysfunction implicated in the pathophysiologic process of schizophrenia [21]. Research into the improvement of cognition in schizophrenia with lamotrigine might lead to better functional outcome in patients with schizophrenia.

Acknowledgements

This study was carried out as Mackinejad's postgraduate thesis. The authors wish to thank Margaret Tejerizo for editing the manuscript.

Highlights

- Cognitive deficit is the core and enduring feature of schizophrenia.
- Lamotrigine is a potential adjunctive treatment strategy for schizophrenia.
- Lamotrigine may improve the attention domain of cognition impairment associated with schizophrenia.

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