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Efficacy of selegiline add on therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study

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Objective It has been reported that selegiline, a Selective Monoamine Oxidase Inhibitor B (MAOI-B), at low doses would be helpful for treating negative symptoms in schizophrenia. Nevertheless, the results are contradictory so far. This study was designed to investigate the effect of selegiline added to risperidone as augmentation therapy in patients with chronic schizophrenia and prominent negative symptoms in an 8 week, double blind and randomized clinical trial.
Methods Eligible participants in this study were 40 patients with chronic schizophrenia. All patients were inpatients and were in the active phase of the illness, and met DSM-IV-TR criteria for schizophrenia. Patients were allocated in a random fashion, 20 to risperidone 6 mg/day plus selegiline 10 mg/day (5 mg bid) and 20 to risperidone 6 mg/day plus placebo. The principal measure of the outcome was Positive and Negative Syndrome Scale (PANSS).
Results Although both protocols significantly decreased the score of the positive, negative, and general psychopathological symptoms over the trial period, the combination of risperidone and selegiline showed a significant superiority over risperidone alone in decreasing negative symptoms and PANSS total scores.
Conclusion The present study indicates selegiline as a potential adjunctive treatment strategy for the negative symptoms of schizophrenia. Nevertheless, results of larger controlled trials are needed before recommendation for a broad clinical application can be made.

KEY WORDS — Monoamine Oxidase Inhibitor-B; selegiline; schizophrenia

INTRODUCTION

Schizophrenia is usually a chronic, lifelong illness with a peak age of onset in the mid-20s. Although the severity of schizophrenia has been recognized for many years, its etiology and pathophysiology are not fully understood (Akhondzadeh, 2006; Mohammadi and Akhondzadeh, 2001). Negative symptoms in schizophrenia broadly comprise blunted affect, apathy, poverty of thought or speech, incoherence, loosening of association, thought-blocking, and social withdrawal (Erhart *et al*., 2006). Negative symptoms have become a special research interest in the last decade because novel atypical antipsychotics have been developed, which claimed to have an improved therapeutic efficacy versus older, typical agents against negative symptoms in patients with schizophrenia (Alvarez *et al*., 2006; Buckley and Stahl, 2007; Javitt, 2001; Möller, 2003, Möller, 2004 2004; Murphy *et al*., 2006). There has been a strong debate

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in the literature on whether antipsychotics can reduce negative symptoms. Currently available treatments for negative symptoms appear to have modest benefits with the result that negative symptoms continue to disproportionately limit patient recovery (Buckley and Stahl, 2007; Murphy *et al*., 2006).

Therefore, it is necessary to look for alternative or additional drug treatment possibilities. It is well known that negative symptoms are related to regional dopamine hypofunction involving prefrontal dopamine projections so it is logical that negative symptoms may be ameliorated via augmentation of dopamine activity (Akhondzadeh, 2006; Javitt, 2001; Möller, 2003). It has been reported that selegiline, a Selective Monoamine Oxidase Inhibitor B (MAOI-B) at low doses would be helpful for treating negative symptoms in schizophrenia (Bodkin *et al*., 1996, 2005; Fohey *et al*., 2007; Gupta *et al*., 1999; Jungerman *et al*., 1999). Nevertheless, the results are contradictory so far. Both positive and negative studies with selegiline have focused on primary negative symptoms and excluded negative symptoms in general. This study was designed to investigate the effect of selegiline added to risperidone as augmentation therapy in patients with chronic schizophrenia and prominent negative symptoms in a double blind and randomized clinical trial.

METHODS

Trial design

This investigation was a prospective, 8 week, double blind study of parallel groups of patients with chronic schizophrenia and was undertaken in three psychiatric hospitals in Tehran, Iran, from December 2005 to May 2007.

Participants

Eligible participants in the study were 40 patients with chronic schizophrenia (11 women and 29 men) with age ranging from 19–44 years. All participants were inpatients, in the active phase of illness, and met DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia. The minimum score of 60 on Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987) and ≥ 15 on negative subscale was required for entry into the study. The patients did not receive narcoleptics from a week prior to entering the trial or depot narcoleptic at least 2 months before the study. Patients were excluded from the study if they had a clinically significant organic and neurological disorder, serious psychotic disorders other than schizophrenia, use of any medications identified as contradicted with selegiline, treatment with antidepressant medication within 1 month of screening, and a current diagnosis of major mood or substance abuse disorder. The PANSS depression item score (exclusion level ≥ 4) was used to exclude patients with significant level of depression. Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (World Medical Association, 2000) and approved by ethics committee at Tehran University of Medical Sciences. Written informed consents were obtained before entering into the study.

INTERVENTION

Patients were randomly allocated 20 to risperidone 6 mg/day plus selegiline 10 mg/day (5 mg bid) (morning and evening) and 20 to risperidone 6 mg/day plus placebo for an 8 week, double-blind, placebo-controlled study. Starting dosage of risperidone was 2 mg/day and was increased to 6 mg/day with 2 mg increments in daily dosage for the first 2 days. Patients in the placebo group received two identical tablets (morning and evening). During the washout period, the patients received benzodiazepine

Table 1. Baseline data

	Selegiline Group	Placebo Group	*p*
Gender	Male: 14, Female: 6	Male: 15, Female: 5	ns
Age (Mean ± SD)	32.70 ± 6.10 (year)	33.65 ± 7.27 (year)	ns
Marital status	Single: 11, Married: 7, Divorced: 2	Single: 10, Married: 7, Divorced: 3	ns
Smoking	14 Patients	15 Patients	ns
Level of education	Under diploma: 14, Diploma: 4, Higher diploma: 2	Under diploma: 13, Diploma: 6, Higher diploma: 1	ns
Duration of illness	85.80 ± 42.21 (month)	92.00 ± 45.49 (month)	ns
Number of life-time hospitalization (Mean ± SD)	4.35 ± 1.87	4.15 ± 1.49	ns

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if necessary. Lorazepam was the drug of choice. Two patients dropped out over the trial (one from each group). Patients also received biperiden if they had faced extrapyramidal symptoms. Patients were assessed by a psychiatrist at baseline and after 2, 4, 6, and 8 weeks after the medication started.

OUTCOME

The principal measure of the 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 patients to treatment. The extrapyramidal symptoms were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) (part one: Parkinsonism, dystonia, dyskinesia, sum of 11 items) (Chouinard *et al*., 1980). Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on days 7, 14, 28, 42, and 56 (Table 2). Patients were randomized to receive selegiline or placebo in a 1: 1 ratio using a computer-generated code. Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments.

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 done 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 tests was performed for 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 side effects between the protocols, Fisher's exact test was performed. Results are presented as mean $\pm$ SEM. Differences were considered significant with $p < 0.05$. For $\alpha = 0.05$, $\beta = 0.2$, to consider a final difference in score between the two groups of at least 5 on the PANSS rating scale, $S = 5$ and power $= 0.8$ (according to the pilot study of this research), the sample size was calculated as at least 15 in each group. Intention to Treat (ITT) analysis with Last Observation Carried Forward (LOCF) procedure was performed.

RESULTS

Seventy-five patients were screened for the study and 40 were randomized to trial medication (20 patients in each group) (Figure 1). No significant differences were identified between patients randomly assigned to the group 1 or 2 condition with regard to basic demographic data including age, age of first onset of illness, gender, marital status, smoking, level of education, mean duration of illness, and number of life-time hospitalization (Table 1).

POSITIVE SYMPTOMS

The mean $\pm$ SEM scores of two groups of patients are shown in Figure 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.84$, df $= 38$, $p = 0.40$). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 2.24$, df $= 1$,

Table 2. Number of patients with side effects

Side effects	Risperidone + Selegiline 10 mg/day	Risperidone + Placebo	*p*
Nausea	6 (%30)	3 (%15)	ns
Insomnia	5 (%25)	2 (%10)	ns
Agitation	5 (%25)	2 (%10)	ns
Hypertension	6 (%30)	2 (%10)	ns
Headache	5 (%25)	3 (%15)	
Tremor	2 (%10)	5 (%25)	ns
Increased appetite	5 (%25)	5 (%25)	ns
Dizziness	2 (%10)	3 (%15)	ns
Abdominal pain	4 (%20)	2 (%10)	ns

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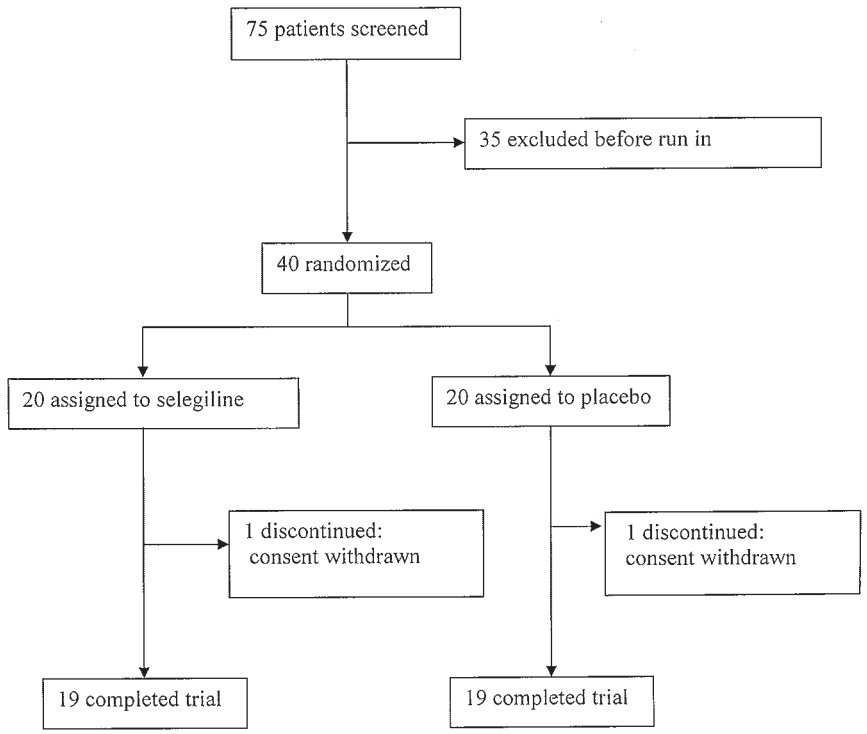

Figure 1. Trial profile

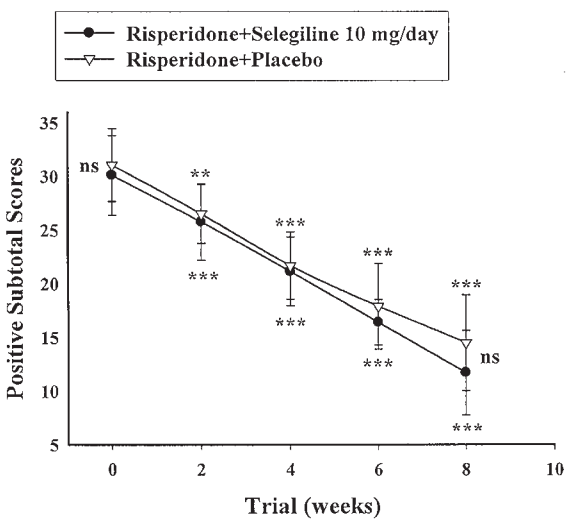

Figure 2. Mean ± SEM of the two protocols on the positive subtotal scores of the PANSS. ns = non-significant; $^{**}<0.01$; and $^{***}<0.001$. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value

$p = 0.14$). The behavior of the two treatment groups was homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 0.75$, $df = 2.07$, $p = 0.47$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the positive subscale scores of PANSS rating scale ($p < 0.0001$). In the selegiline and placebo groups, *post-hoc* comparisons showed a significant change from week 2. The difference between the two treatments was not significant at the endpoint (week 8) ($t = 0.92$, $df = 38$, $p = 0.36$).

NEGATIVE 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 ($t = 0.66$, $df = 38$, $p = 0.51$). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 4.19$, $df = 1$, $p = 0.04$). The behavior of the two treatment groups

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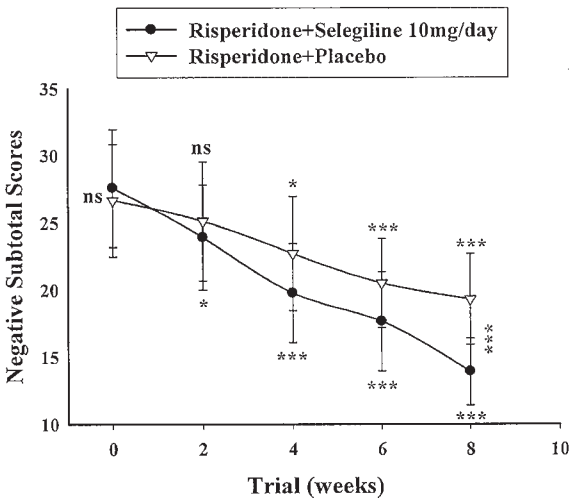

Figure 3. Mean ± SEM of the two protocols on the negative subtotal scores of the PANSS. ns = non-significant; *<0.05; and ***<0.001. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value and vertical symbols were used for between group comparisons

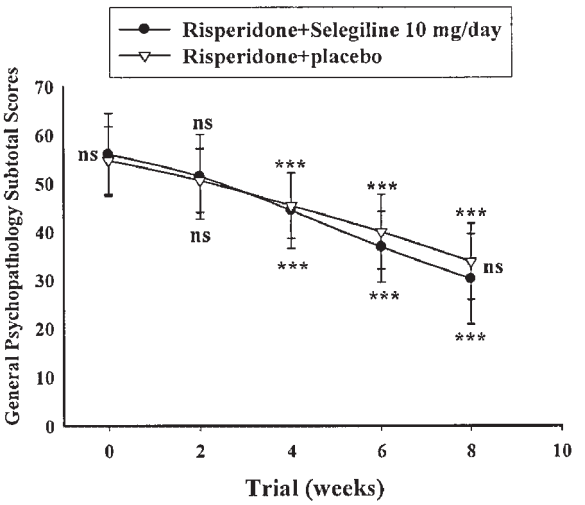

Figure 4. Mean ± SEM of the two protocols on the general psychopathology subtotal scores of the PANSS. ns = non-significant and ***<0.001. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value

was not homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 18.63$, $df = 2.42$, $p < 0.001$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the negative subscale scores of PANSS rating scale ($p < 0.0001$). In the selegiline and placebo group, *post-hoc* comparisons showed a significant change from week 2 and 4, respectively. The difference between the two treatments was significant at the endpoint (week 8) ($t = 5.23$, $df = 38$, $p < 0.001$). The changes at the endpoint compared to baseline were: -13.65 ± 3.96 (mean ± SD) and -7.85 ± 2.70 for selegiline and placebo, respectively. A significant difference was observed on the change of scores of the negative subscale of PANSS rating scale at week 8 compared to baseline in the two groups ($t = 5.40$, $df = 38$, $p < 0.001$).

GENERAL PSYCHOPATHOLOGICAL SYMPTOMS

The mean ± SEM scores of two groups of patients are shown in Figure 4. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.61$, $df = 38$, $p = 0.59$). The difference between the two treatments was not significant as indicated by the effect of group, the between subjects factor (Greenhouse–Geisser corrected: $F = 0.28$, $df = 1$, $p = 0.59$). The behavior of the two treatment groups was homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected: $F = 2.47$, $df = 1.45$, $p = 0.11$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the general psychopathological symptoms subscale scores of PANSS rating scale ($p < 0.0001$). In both groups *post-hoc* comparisons showed a significant change from week 4. The difference between the two treatments was not significant at the endpoint (week 8) ($t = 1.01$, $df = 38$, $p = 0.31$). In addition, there was no significant deference between the two groups in terms of depressed mood (item 6 in this subscale).

PANSS TOTAL SCORES

The mean ± SEM scores of two groups are shown in Figure 5. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t = 0.24$, $df = 38$, $p = 0.80$). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 3.80$, $df = 1$, $p = 0.05$). The behavior of the two treatment groups was not homogeneous across time (groups-by-time interaction, Greenhouse–Geisser corrected:

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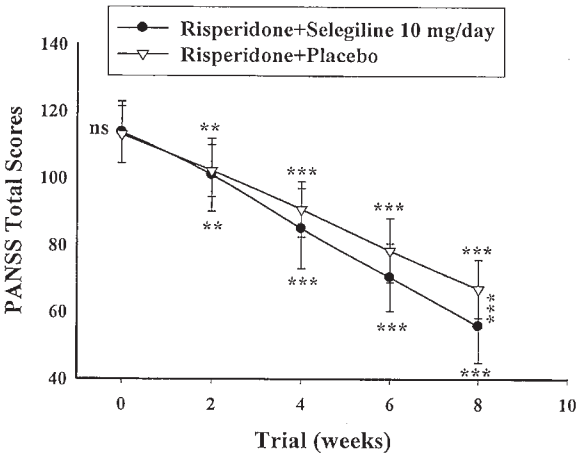

Figure 5. Mean ± SEM of the two protocols on the total scores of the PANSS. ns = non-significant; $^{**}<0.01$; and $^{***}<0.001$. The horizontal symbols (***) were used to express statistical significance versus their respective baseline value and vertical symbols were used for between group comparisons

$F = 6.92$, $df = 1.77$; $p = 0.003$). In addition, a one-way repeated measures analysis of variance showed a significant effect of both treatments on the total scores of PANSS rating scale ($p < 0.0001$). In both groups *post-hoc* comparisons showed a significant change from week 2. The difference between the two treatments was significant at the endpoint (week 8) ($t = 2.82$, $df = 38$, $p = 0.007$). The changes at the endpoint compared to baseline were: -55.00 ± 12.72 (mean ± SD) and -46.00 ± 11.48 for selegiline and placebo, respectively. A significant difference was observed on the change of scores of the PANSS total at week 8 compared to baseline in the two groups ($t = 2.34$, $df = 38$, $p = 0.02$).

EXTRAPYRAMIDAL SYMPTOMS RATING SCALE

Although the means ESRS scores for the placebo group were higher than selegiline group over the 8 weeks of trial, the difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (Greenhouse–Geisser corrected: $F = 2.71$, $df = 1$, $p = 0.10$). Nevertheless, a significant difference was observed between the overall mean biperiden dosages (mg) in two groups (86.20 ± 100.89 and 140.45 ± 70.38 for selegiline and placebo group, respectively; mean ± SD) ($p = 0.05$; $t = 1.97$; $df = 38$). In addition, the difference between the two treatments in terms of the number of days of biperiden treatment was significant (13.84 ± 16.53 and 23.25 ± 11.55 for selegiline and placebo group, respectively; mean ± SD) ($p = 0.04$; $t = 2.08$; $df = 38$).

CLINICAL COMPLICATIONS AND SIDE EFFECTS

Nine side effects were observed over the trial. The difference between the selegiline and placebo in the frequency of side effects was not significant (Table 2). None of patients who received selegiline had increased blood pressure.

DISCUSSION

Negative symptoms are a source of important morbidity in schizophrenia therefore; developing effective treatments for them is a matter of substantial concern (Tattan and Creed, 2001). Atypical antipsychotic medications are often distinguished from conventional antipsychotics based on clinical advantages such as a low potential for causing extrapyramidal symptoms and efficacy for the negative symptoms of schizophrenia (Murphy *et al*., 2006). But the debate surrounding the efficacy of atypical antipsychotics on negative symptoms has been fuelled by contradictory findings. It has been reported that use of the dopaminergic antiparkinsonian drug selegiline, a MAOI-B, at low doses would be helpful for treating negative symptoms in schizophrenia (Bodkin *et al*., 1996, 2005; Fohey *et al*., 2007; Gupta *et al*., 1999).

As expected, in this study both groups of schizophrenic patients showed significant improvement on the PANSS total scores and on all subscales during the 8 weeks of treatment with risperidone. In agreement with our hypothesis, the selegiline group had significantly greater improvement in the negative symptoms over 8 weeks trial. No significant differences were observed between the means of the two groups on the positive and general psychopathology scores. Clinical characteristics of the schizophrenic patients, such as sex, age, and duration of illness, did not differ between groups and cannot explain differences in the therapeutic outcome. The use of biperiden was greater in the group receiving risperidone plus placebo and the difference was significant. The beneficial effect of selegiline on negative symptoms of schizophrenia may be suggesting the role of dopaminergic hypofunction in negative. The result of the present trial is in line with a couple of reported studies that suggested selegiline augmentation of antipsychotic medication in patients suffering from schizophrenia with negative symptoms (Bodkin

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et al., 1996, 2005; Gupta *et al*., 1999). Nevertheless, in this trial we found selegiline at this dose decreased the use of biperiden (Bodkin *et al*., 2005). One of the concerns regarding dopamineregic agents in schizophrenia is exacerbation of positive symptoms. However, selegiline at this dose did not exacerbate positive symptoms. It should be noted that patients in this study were in active phase of illness and they were not stable on risperidone. Since the trial was carried out in patients experiencing both negative and positive symptoms during acute exacerbation of schizophrenic psychoses, the question arises whether only those negative symptoms that were secondary to positive symptoms were reduced. Nevertheless, this methodologic feature may also enhance the generalizability of these findings since optimal treatment of negative symptoms in general is important since they are associated with poor outcome and long-term disability. Effective treatment at the earliest phase of illness appears to be an important strategy in improving global outcome (Tattan and Creed, 2001). Therapy with 10 mg/day of selegilne was well tolerated, and no clinically important side effects were observed. The therapeutic benefit of the combined therapy has to be attributed to effects of selegiline. The limitations of the present study, including the short period of study, only patients with chronic schizophrenia and a fixed dose of selegiline should be taken into account and this indicates the need for further research.

CONCLUSION

In conclusion, the present study indicates selegiline as a potential adjunctive treatment strategy for treatment of negative symptoms of schizophrenia. Nevertheless, results of larger controlled trials are needed, before recommendation for a broad clinical application can be made.

THE TRIAL GROUP

Shahin Akhondzadeh: principal investigator and statistical support, clinical neuropsychopharmacologist from December 2005 to May 2007. Afshar Amiri: resident of psychiatry, trialist from December 2005 to May 2007. Mohammad Hajiazim: clinical coordinator, psychiatrist from December 2005 to May 2007. Mohammad-Reza Khodaie-Ardakani: clinical coordinator, psychiatrist from December 2005 to May 2007. Mohammad-Kamran Derakhshan: resident of psychiatry, trialist from December 2005 to May 2007. Ahmad-Ali Noorbala: clinical coordinator, psychiatrist from December 2005 to May 2007. Ali-Akbar Nejatisafa: clinical coordinator, psychiatrist from December 2005 to May 2007.Maedeh Raznahan: statistical support, from December 2005 to May 2007.

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