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ORIGINAL INVESTIGATION

A placebo-controlled study of the modafinil added to risperidone in chronic schizophrenia

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Abstract
Rational In recent years, evidence suggests that modafinil may be useful for certain symptom domains of schizophrenia, especially for the negative and cognitive symptoms. However, the results are not consistent.
Objective This study was designed to investigate the effect of modafinil added to risperidone in patients with chronic schizophrenia in a double blind and randomized clinical trial.
Methods Participants were inpatients males (35) and females (11), ages 20–49 years at two teaching psychiatric hospital in Iran. All patients were in the active phase of the illness and met DSM-IV-TR criteria for schizophrenia. Patients were allocated in a random fashion 23 patients to risperidone 6 mg/day plus modafinil 200 mg/day and 23 patients to risperidone 6 mg/day plus placebo. The principal measure of outcome was the positive and negative syndrome scale (PANSS). Patients were assessed by a psychiatrist at baseline and after 2, 4, 6 and 8 weeks after the start of medication.
Results The modafinil group had significantly greater improvement in the negative symptoms as well as PANSS total scores over the 8-week trial. Therapy with 200 mg/day of modafinil was well tolerated and no clinically important side effects were observed.
Conclusion The present study indicates modafinil as a potential adjunctive treatment strategy for treatment of schizophrenia particularly the negative symptoms. Nevertheless, results of larger-controlled trials are needed before recommendation for broad clinical application can be made. This trial is registered with the Iranian Clinical Trials Registry (IRCT138903131556N16).

Keywords Chronic schizophrenia · Modafinil · Negative symptoms

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Introduction

Schizophrenia is conceptualized as a disease process with multiple causal factors and is characterized by multiple signs and symptoms involving thought, perception, emotion and motor activity (Mohammadi and Akhondzadeh 2001; Akhondzadeh 2006). Treatment involves combination of psychosocial rehabilitation and pharmacotherapy. In most cases, chronic antipsychotic therapy is required to treat symptoms, avoid relapse and attenuate episode recurrence (Mohammadi and Akhondzadeh 2001; Akhondzadeh 2006). Despite the growing number of pharmacologic agents for the treatment of schizophrenia, many patients do not adequately benefit from or tolerate currently available antipsychotics (Buckley and Stahl 2007). Existing

typical and atypical antipsychotic medications are relatively equally effective in treating what are known as the positive symptoms of schizophrenia. What has been prominently lacking, however, is an agent that also treats the negative symptoms as well as substantial cognitive impairment (Buckley and Stahl 2007; Akhondzadeh et al. 2011). Indeed, persistent negative and cognitive symptoms of schizophrenia are a major cause of chronic morbidity and poor long-term outcome (Buckley and Stahl 2007; Akhondzadeh et al. 2011). The recognition that this is a major shortfall in current treatment options has fuelled renewed interest in developing better treatments for negative symptoms (Akhondzadeh 2006).

Modafinil is a wake-promoting agent in which pharmacological mechanisms are distinct from those of conventional psychostimulants (Ballon and Feifel 2006). Modafinil has been tested for efficacy as an augmenting agent to target-specific residual symptoms of depression such as fatigue and sleepiness (Abolfazli et al. 2011). Although its mechanism of action is not fully understood, modafinil seems to alter the balance of γ-aminobutyric acid (GABA) and glutamate, resulting in activation of the hypothalamus (Ballon and Feifel 2006). It also increases metabolic rate in the centrolateral thalamus, the central nucleus of the amygdala and the hippocampus (Ballon and Feifel 2006). Modafinil has been tested for efficacy as an augmenting agent to treat major depression or as the treatment of ADHD (Amiri et al. 2008; Kahbazi et al. 2009; Abolfazli et al. 2011).

In recent years, evidence suggests that modafinil may also be useful for certain symptom domains of schizophrenia especially for the negative and cognitive symptoms (Kumar 2008; Minzenberg and Carter 2008; Saavedra-Velez et al. 2009). Modafinil increases extracellular level of dopamine in the prefrontal cortex (Zara de Saint et al. 2001). Therefore, potentially, it can reduce negative symptoms in schizophrenia.

Pierre et al. (2007) reported use of modafinil adjunctive therapy (200 mg/day). Twenty subjects were enrolled (n= 10 for modafinil, n=10 for placebo). There was no significant difference between modafinil and placebo for changes in the negative symptom ratings, the primary study endpoint. However, modafinil treatment was associated with a greater rate and degree of global improvement at the study endpoint compared with placebo. No significant worsening of psychopathology was observed and modafinil was well tolerated. Although no effect on negative symptoms was found, adjunctive therapy with modafinil may result in global improvements in patients with schizophrenia who have prominent negative symptoms. In addition, modafinil has been suggested to alleviate fatigue and possibly neurocognitive deficits in schizophrenia as well as negative symptoms (Rosenthal and Bryant 2004; Turner et al. 2004; Spence et al. 2005). These findings support additional research into a potential role for modafinil in the treatment of schizophrenia and, in particular, negative symptoms. This study was designed to investigate the effect of modafinil added to risperidone as adjunctive therapy in patients with chronic schizophrenia and prominent negative symptoms in a double-blind and randomized clinical trial.

Methods

Trial setting

The trial was a prospective, 8-week, double-blind study of parallel groups of patients with chronic schizophrenia and was undertaken in two psychiatric hospitals in Iran from January 2008 to January 2011.

Participants

Eligible participants in the study were 46 patients with chronic schizophrenia (11 women and 35 men) with ages ranging from 20 to 49 years (Table 1). All participants were inpatients (over the period of study), in the active phase of illness, and met DSM-IV-TR (American Psychiatric Association 2000) criteria for schizophrenia (based on the structured clinical interview for DSM-IV). Minimum score of 60 on the positive and negative syndrome scale (PANSS; Kay et al. 1987; range: 84–127) and ≥20 on the negative subscale (range: 20–37) was required for entry into the study (Ghaleiha et al. 2010). The patients did not receive neuroleptics for a week prior to entering the trial or long-acting antipsychotics at least 2 months before the study. Patients were excluded from the study if they had clinically significant organic and neurological disorder, serious psychotic disorders other than schizophrenia, use of any medications identified as contraindicated with modafinil, 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. The PANSS depression item assess feeling of sadness, discouragement, helplessness and pessimism based on verbal report of depressed mood during the course of interview and on observed influence on attitude and behavior. Pregnant or lactating women and those of reproductive age without adequate contraception were also excluded. Additional exclusion criteria were hypertension, hypotension and habitual consumption of more than 250 mg/day of caffeine. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the ethics committee of Tehran University of Medical Sciences (grant no. 6157). Written informed consents were obtained before entering into the study.

Table 1 Baseline data

	Modafinil group	Placebo group	*P* values
Gender	Male: 18	Male: 17	1.00
	Female:5	Female: 6	
Age (mean ± SD)	33.52±5.28 years	34.08±6.34 years	0.74
Marital status	Single: 10	Single: 11	1.00
	Married: 8	Married: 9	
	Divorced: 5	Divorced: 3	
Level of education	Under diploma: 16	Under diploma: 16	1.00
	Diploma: 5	Diploma: 6	
	Higher diploma: 2	Higher diploma: 1	
Duration of illness (month)	96.08±38.70	86.82±42.80	0.44
Number of lifetime hospitalization (mean ± SD)	4.49±1.72	4.13±1.57	0.59
Baseline PANSS total score	113.21±8.6410	114.34±9.59	0.67
Baseline positive subscale score	30.60±3.75	31.60±3.65	0.36
Baseline negative subscale score	27.04±4.76	27.30±4.49	0.84
Baseline general psychopathology subscale score	55.56±7.86	55.00±6.91	0.79
Prior antipsychotic medications	Haloperidol: 12	Haloperidol: 13	1.00
	Flufenazine: 6	Flufenazine: 7	
	Risperidone: 15	Risperidone: 16	
	Olanzapine: 7	Olanzapine: 5	

Intervention

Twenty-three patients were randomly allocated to risperidone (6 mg/day) plus modafinil, 200 mg/day (100 mg mid-morning and evening) and 23 patients were allocated 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 in 2 mg increments daily to 6 mg/day. Patients in the placebo group received two identical capsules (morning and evening). The patients had a 1-week antipsychotic washout period before entering the study. During the washout period, the patients received benzodiazepine if necessary and lorazepam was the drug of choice. Benzodiazepine was not allowed after randomization. Four patients dropped out of the study (one patient from the modafinil group and three patients from the placebo group). Patients also received biperiden if they faced extrapyramidal symptoms. Patients were assessed by a psychiatrist at baseline and after 2, 4, 6 and 8 weeks after the start of medication.

Outcome

The principal measure of outcome was the PANSS that has been used in several studies in Iran (Akhondzadeh et al. 2006, 2007). PANSS total score was considered as primary efficacy, and secondary efficacy parameters included the PANSS subscales. The PANSS includes 30 items on three subscales, 7 items covering positive symptoms, 7 items covering negative symptoms and 16 items covering general psychopathology. In addition, a total score presents all three parts (Kay et al. 1987). The raters used standardized instructions in the use of PANSS. The mean decrease in the PANSS score from baseline was used as the main outcome measure of patient response to treatment. Treatment response was defined as at least 50% improvement in the PANSS total score (Akhondzadeh et al. 2011). Inter-rater reliability for the PANSS was greater than 0.82. 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 psychiatrist on days 7, 14, 28, 42 and 56 (Table 3). The side-effect checklist was a 25-item somatic complaint questionnaire. The checklist included a range of somatic complaints: nausea, headache, drowsiness, dizziness, tremor, change in weight, etc. Patients were randomized to receive modafinil or placebo in a 1:1 ratio using a computer-generated code and the randomization was stratified by site. The assignments were kept in sealed opaque envelopes until data analysis. 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. Two groups were considered between-subjects factor and five measurements during

treatment was considered the within-subjects factor (time). This was done for positive, negative, general psychopathology subscale and PANSS total scores. A Greenhouse–Geisser correction was used for sphericity. To compare the two groups at baseline and at 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 the frequency of side effects between the protocols, Fisher's exact test was performed. Results are presented as mean ± SD. Differences were considered significant with $P<0.05$. To consider $\alpha=0.05$ and $\beta=0.2$, the final difference between the two groups was calculated to be at least a score of 5 on the Negative subscale of PANSS rating scale, $S=5$ and power=0.8 (based on a pilot study for this project). The sample size was calculated to be at least 15 in each group. Intention to treat (ITT) analysis with last observation carried forward (LOCF) procedure (that is a conservative approach for ITT) was performed. Data were analyzed using commercially available statistical packages (SPSS 13.00. Chicago, IL, USA).

Results

Patient disposition and characteristics

A number of 74 patients were screened for the study and 46 were randomized to groups for trial medication (23 patients in each group; Fig. 1). For this study, 20 patients from Kurdistan University of Medical Sciences and 26 patients from Roozbeh psychiatric hospital were recruited. No significant difference was 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, level of education and mean duration of illness (Table 1). During the washout period, six patients from the modafinil group and eight patients from the placebo group received lorazapam.

PANSS total scores

The mean ± SD scores of the two groups of patients are shown in Table 2 and Fig. 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS ($t=0.42$, $df=44$, $P=0.67$). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor ($F=4.81$, $df=1$, $P=0.034$). The efficacy pattern of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected values: $F=4.22$, $df=1.75$, $P=0.022$). The change in the PANSS total score between the two treatment groups at endpoint was significant ($t=2.86$, $df=44$, $P=0.006$). The changes at endpoint compared to baseline were: -56.73±15.01 (mean ±SD) and −47.82±10.49 for modafinil and placebo, respectively. A significant difference was observed on PANSS total score at week 8 compared to baseline in the two groups ($t=2.33$, $df=44$, $P=0.02$). The modafinil group (65%) and the placebo group (30%) responded to treatment (at least 50% reductions in the PANSS total score).

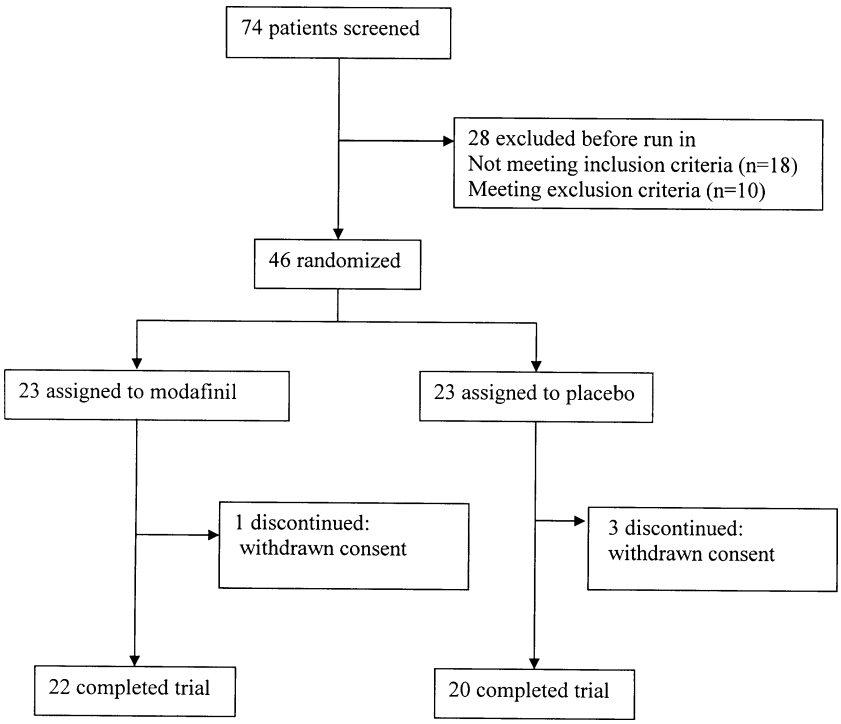

Fig. 1 Trial profile

Table 2 Mean ± SD of the two protocols on the total PANSS scores and its three subscales

	Week 0	Week 2	Week 4	Week 6	Week 8	*P* values
Positive subscale of PANSS						
Risperidone + modafinil	30.60±3.75	26.08±3.54	21.13±3.81	16.26±4.31	11.86±5.77	0.11
Risperidone + placebo	31.60±3.60	26.78±2.90	22.26±3.31	18.26±4.02	14.34±4.54	
Negative subscale of PANSS						
Risperidone + modafinil	27.04±4.76	23.65±4.19	19.91±3.72	18.13±4.19	15.13±4.30	0.03
Risperidone + placebo	27.30±4.49	25.69±4.62	22.69±4.18	20.34±3.47	18.73±4.11	
General psychopathology subscale of PANSS						
Risperidone + modafinil	55.56±7.86	50.04±8.41	43.60±8.18	35.56±9.04	28.82±10.96	0.27
Risperidone + placebo	55.00±6.91	50.82±7.08	45.86±8.19	40.30±9.62	34.08±11.37	
PANSS total score						
Risperidone + modafinil	113.21±8.64	99.69±10.24	84.39±12.12	69.47±12.05	56.47±13.47	0.034
Risperidone + placebo	114.34±9.50	102.21±8.16	90.52±8.74	78.21±10.67	66.52±10.07	

Positive symptoms

The mean ± SD scores of two groups of patients are shown in Table 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS (t=0.91, df=44, P=0.36). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (F=2.621, df=1, P=0.11). The efficacy pattern of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected values: F=0.73, df=1.85; P=0.47). The change in the positive subscale of PANSS between the two treatment groups at endpoint was not significant (t=1.61, df=44, P=0.11)

Negative symptoms

The mean ± SD scores of the two groups of patients are shown in Table 2 and Fig. 3. There were no significant differences between the two groups at week 0 (baseline) on the PANSS (t=0.19, df=44, P=0.84). The difference between the two treatments was significant as indicated by the effect of group, the between-subjects factor (F=3.79, df=1; P=0.03). The efficacy pattern of the two treatment groups was not similar across time (groups-by-time interaction, Greenhouse–Geisser corrected values: F=4.12, df=1.67, P=0.026). The change in the negative subscale of PANSS between the two treatment groups at endpoint was significant (t=2.90, df=44, P=0.005). The changes at the

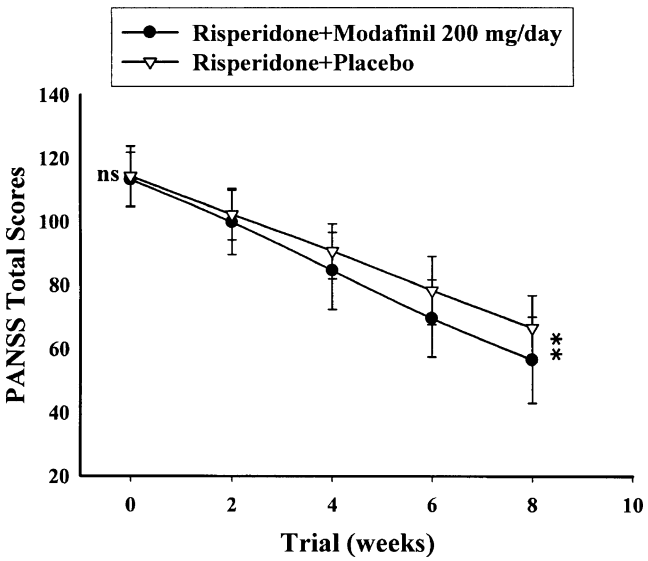

Fig. 2 Mean ± SD of the two protocols on the total scores of the PANSS. *ns* Nonsignificant and **<0.01

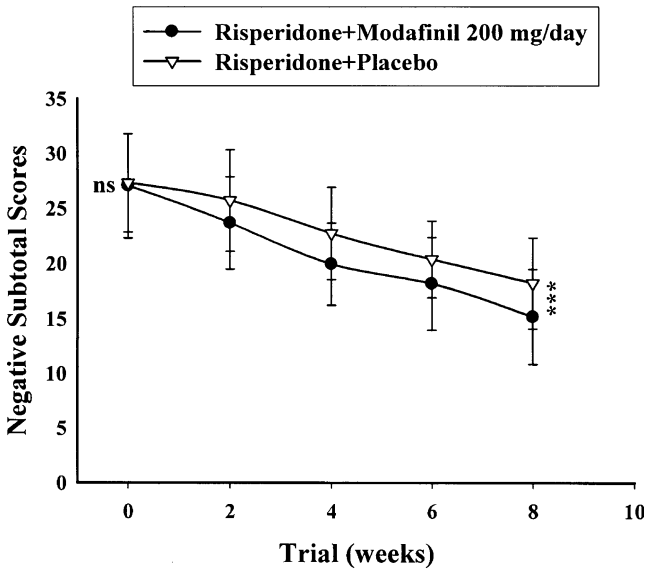

Fig. 3 Mean ± SD of the two protocols on the negative subtotal scores of the PANSS. ns Nonsignificant and ***<0.001

endpoint compared to baseline were: -11.91±4.96 (mean± SD) and −8.56±3.91 for modafinil and placebo, respectively. A significant difference was observed on the negative subscale of PANSS at week 8 compared to baseline in the two groups (t=2.53, df=44, P=0.01).

General psychopathological symptoms

The mean ± SD scores of the two groups of patients are shown in Table 2. There were no significant differences between the two groups at week 0 (baseline) on the PANSS (t=0.25, df=44, P=0.79). The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (F=1.21, df=1, P=0.27). The efficacy pattern of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected values: F=2.92, df=1.40, P=0.078). The change in the general psychopathological score between the two treatment groups at endpoint was not significant (t=1.59, df=44, P=0.11)

Extrapyramidal symptoms rating scale

The difference between the two treatments was not significant as indicated by the effect of group, the between-subjects factor (F=0.62, df=1, P=0.43). The pattern of the two treatment groups was similar across time (groups-by-time interaction, Greenhouse–Geisser corrected values: F=0.94; df=1.44, P=0.36). No significant difference was observed between the overall mean biperiden dosages (mg) in two groups (119.56±92.18 and 112.69±89.62 for the modafinil and the placebo groups, respectively; mean ± SD). Moreover, the difference between the two treatments in terms of number of biperiden treatment days was not significant (16.17±13.54 for modafinil group and 15.32±13.92 for placebo group; mean ± SD).

Clinical complications and side effects

Nine types of side effects were observed over the trial. The difference between the modafinil and placebo in the frequency of side effects was not significant (Table 3). Each group (100%) had at least one adverse event over the trial period.

Table 3 Number of patients with side effects over the 8 weeks of trial

Side effects	Risperidone + modafinil (200 mg/day)	Risperidone + placebo	P values
Nausea	6 (26%)	4 (17%)	0.72
Insomnia	4 (17%)	3 (%13)	1.00
Dizziness	5 (22%)	3 (13%)	0.69
Headache	5(22%)	3(13%)	0.69
Tremor	4 (17%)	2 (9 %)	0.66
Drowsiness	5 (22%)	2 (9%)	0.41
Sedation	3 (13%)	5 (22%)	0.69
Weight gain	2 (13%)	4 (17%)	0.66
Sexual dysfunction	2 (13%)	2 (13%)	1.00

Discussion

Despite current medical treatments and the fact that schizophrenia affects only about 1% of the population, it is one of the costliest diseases worldwide (Akhondzadeh 2006). The two studied groups showed significant improvement on the PANSS total score and on all subscales during the 8-week treatment with risperidone based on the results of this study. In agreement with our hypothesis, the modafinil group had significantly greater improvement in the negative symptoms as well as total score of PANSS over the 8-week trial. Clinical characteristics of the schizophrenic patients, such as sex, age duration of illness and prior antipsychotic medications, did not differ between groups and cannot explain differences in the therapeutic outcome. Therapy with 200 mg/day of modafinil was well tolerated, and no major clinical side effects were observed. Nevertheless, it may be possible that the study was relatively small to determine differences in side effect rates, and this should be considered as a limitation of this study. To the best of our knowledge, there is no report regarding kinetic interactions between modafinil and atypical antipsychotics leading us to assume that the therapeutic effect shown by modafinil on symptoms of schizophrenia is likely to result from a pharmacodynamic mechanism. Since the negative symptoms of schizophrenia may be related to dopaminergic hypofunction in the prefrontal cortex (Akhondzadeh 2006), drugs, such as modafinil, that increase dopaminergic activity should theoretically decrease negative symptoms (Zara de Saint et al. 2001). In a 4-week, uncontrolled, open-label, pilot study that evaluated adjunctive modafinil in patients with schizophrenia or schizoaffective disorder, significant improvement was seen in global functioning, as well as fatigue, negative symptoms and cognitive function, while maintaining positive symptom stability (Rosenthal and Bryant 2004). Results of the present trial are in line with this study. In addition, Pierre et al., in an 8-week double-blind and placebo-controlled study reported no effect of modafinil on negative symptoms, which may be due to small sample size and there may be not enough statistical power for finding a difference in negative symptoms. However, they mentioned that ad-

junctive therapy with modafinil may result in global improvements in patients with schizophrenia who have prominent negative symptoms. They observed a significant difference in the mean endpoint clinical global improvement score. In addition, Kane et al., in a 4-week, randomized and placebo controlled, proof-of-concept study reported that adjuctive armodafinil, the longer-lasting isomer of modafinil, was not associated with an improvement in cognitive measures in adults with schizophrenia, but armodafinil 200 mg/day appeared to mitigated the negative symptoms and PANSS total score and armodafinil was generally well tolerated (Kane et al. 2010). Our results regarding negative symptoms and PANSS total score are in line with armodafinil study. In addition, Freudenreich et al. in a double-blind, placebo-controlled, flexible-dosed 8-week pilot trial added modafinil up to 300 mg/day to stabilized schizophrenia outpatients receiving clozapine. Psychopathology, cognition and wakefulness/fatigue were assessed (Freudenreich et al. 2009). However, the results of this pilot trial did not support routine use of modafinil to treat negative symptoms, cognitive deficits or wakefulness/fatigue in patients on clozapine. Nevertheless, modafinil was well tolerated and did not worsen psychosis. Although there are some case reports regarding modafinil-induced psychosis (Mariani and Hart 2005; Wu et al. 2008), in our study, modafinil did not worsen positive symptoms and our results are consistent with previous reports (Pierre et al. 2007). 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). In addition, we had a controlled arm with similar characteristics regarding positive symptoms and extrapyramidal symptoms. On the other hand, the exclusion of individuals with high levels of depression would be expected to limit endpoint regarding secondary negative symptoms due to depression and help ensure that measured changes in negative symptoms were not really due to reduced depressive symptom burden.

A relatively short duration of study, limitation of the study group to chronic schizophrenia patients and use of a fixed dose of modafinil should be taken into account as the limitation of the present study; this indicates the need for further research.

Conclusion

In summary, the present study indicates modafinil as a potential adjunctive treatment strategy for the treatment of schizophrenia and, in particular, for the treatment of its negative symptoms. Nevertheless, results of larger-controlled trials are needed before recommendation for broad clinical application can be made.

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Conflicts of interest None

References

Abolfazli R, Hosseini M, Ghanizadeh A, Ghaleiha A, Tabrizi M, Raznahan M, Golalizadeh M, Akhondzadeh S (2011) Double-blind randomized parallel-group clinical trial of efficacy of the combination fluoxetine plus modafinil versus fluoxetine plus placebo in the treatment of major depression. Depress Anxiety 28:297–302

Akhondzadeh S (2006) Pharmacotherapy of schizophrenia: the past, present and future. Curr Drug Therapy 1:1–7

Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH (2006) Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res 84:405–410

Akhondzadeh S, Tabatabaee M, Amini H, Ahmadi-Abhari SA, Abbasi SH, Behnam B (2007) Celecoxib as adjunctive therapy in schizophrenia: a double-blind, randomized and placebo-controlled trial. Schizophr Res 90:179–185

Akhondzadeh S, Ghayyoumi R, Rezaei F, Salehi B, Modabbernia AH, Maroufi A, Esfandiari GR, Naderi M, Ghebleh F, Tabrizi M, Rezazadeh SA (2011) Sildenafil adjunctive therapy to risperidone in the treatment of the negative symptoms of schizophrenia: a double-blind randomized placebo-controlled trial. Psychopharmacology 213:809–815

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn., text revision. American Psychiatric Association, Washington, DC

Amiri S, Mohammadi MR, Mohammadi M, Nouroozinejad GH, Kahbazi M, Akhondzadeh S (2008) Modafinil as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry 32:145–149

Ballon JS, Feifel D (2006) A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 67:554–666

Buckley PF, Stahl SM (2007) Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or cul-de-sac? Acta Psychiatr Scand 115:93–100

Chouinard G, Ross-Chouinard A, Annables L, Jones BD (1980) Extrapyramidal symptoms rating scale (abstract). Can J Neurol Sci 7:233

de Saint ZH, Martine O, Claude R, Gérard B, Stylianos N (2001) Variations in extracellular monoamines in the prefrontal cortex and medial hypothalamus after modafinil administration: a microdialysis study in rats. Neuroreport 12:3533–3537

Freudenreich O, Henderson DC, Macklin EA, Evins AE, Fan X, Cather C, Walsh JP, Goff DC (2009) Modafinil for clozapine-treated schizophrenia patie6nts: a double-blind, placebo-controlled pilot trial. J Clin Psychiatry 70:1674–1680

Ghaleiha A, Noorbala AA, Farnaghi F, Hajiazim M, Akhondzadeh S (2010) A double-blind, randomized, and placebo-controlled trial of buspirone added to risperidone in patients with chronic schizophrenia. J Clin Psychopharmacol 30:678–682

Kahbazi M, Ghoreishi A, Rahiminejad F, Mohammadi MR, Kamalipour A, Akhondzadeh S (2009) A randomized, double-blind and placebo-controlled trial of modafinil in children and adolescents with attention deficit and hyperactivity disorder. Psychiatry Res 168:234–237

Kane JM, D'Souza DC, Patkar AA, Youakim JM, Tiller JM, Yang R, Keefe RS (2010) Armodafinil as adjunctive therapy in adults with cognitive deficits associated with schizophrenia: a 4-week, double-blind, placebo-controlled study. J Clin Psychiatry 71:1475–1481

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale for schizophrenia. Schizophrenia Bull 13:261–276

Kumar R (2008) Approved and investigational uses of modafinil: an evidence-based review. Drugs 68:1803–1839

Mariani JJ, Hart CL (2005) Psychosis associated with modafinil and shift work. Am J Psychiatry 162:1983

Minzenberg MJ, Carter CS (2008) Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33:1477–1502

Mohammadi MR, Akhondzadeh S (2001) Schizophrenia: etiology and pharmacotherapy I. Drugs 4:1167–1172

Pierre JM, Peloian JH, Wirshing DA, Wirshing WC, Marder SR (2007) A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. J Clin Psychiatry 68:705–710

Rosenthal MH, Bryant SL (2004) Benefits of adjunct modafinil in an open-label, pilot study in patients with schizophrenia. Clin Neuropharmacol 27:38–43

Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer JP (2009) Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. J Clin Psychiatry 70:104–112

Spence SA, Green RD, Wilkinson ID, Hunter MD (2005) Modafinil modulates anterior cingulate function in chronic schizophrenia. Br J Psychiatry 187:55–61

Tattan TM, Creed FH (2001) Negative symptoms of schizophrenia and compliance with medication. Schizophr Bull 27:149–155

Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ (2004) Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology 29:1363–1373

Wu P, Jones S, Ryan CJ, Michail D, Robinson TD (2008) Modafinil-induced psychosis. Intern Med J 38:677–678