

Selegiline in Comparison with Methylphenidate in Treatment of Adults with Attention Deficit Hyperactivity Disorder: A Double-blind, Randomized Trial

Mohammad Mohammadi, MD^{1,2}
Shahin Akhondzadeh, PhD²
Farbod Fadai, MD^{1,3}
Mohammad Reza Mohammadi, MD²

1 Islamic Azad University, Medical Sciences Branch of Tehran, Tehran, Iran

2 Psychiatry & Psychology Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran

3 University of Social Welfare and Rehabilitation Sciences, Razi Hospital Tehran, Iran

Corresponding author:

Mohammad Mohammadi,
Psychiatric Research Center,
Tehran University of Medical Sciences,
Roozbeh Hospital,
South Kargar Ave. 1333 795914
Tehran, Iran
Tel:+98-21-55413540
Fax:+98-21-55421959
E-mail:
dr.m.mohamadii@gmail.com

Objective: Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental disorders in childhood and it continues to adulthood without proper treatment. Stimulants have been used in treatment of ADHD for many years and the efficacy of methylphenidate (MPH) in the treatment of adults with ADHD has been proven to be acceptable according to meta-analysis studies. However, there are some concerns about stimulants. Finding other effective medications for the treatment of adult ADHD seems necessary. We tried a monoamine oxidase inhibitor, Selegiline, as there are some theoretical and experimental evidences for the efficacy of this medication .

Method: Forty patients were randomized to receive Selegiline or methylphenidate in an equal ratio for an 8-week double-blind clinical trial. Each patient filled the CAARS self report screening form before starting to take the medication and in weeks 2-4-6 and 8. Patients were also assessed by a psychiatrist at the baseline and on each 14 days up to the 8 weeks period.

Results: The mean score of the two groups- receiving Selegiline or methylphenidate- decreased over the 8 weeks. There was not a significant difference between the two groups. The most prevalent side-effect of methylphenidate was decrease of appetite and for Selegiline change in sleep pattern .

Conclusion: Selegiline is as effective as methylphenidate in the treatment of adults with Attention-Deficit/Hyperactivity Disorder. Selegiline can be an alternative medication for the treatment of adult ADHD If its clinical efficacy is proven by other larger studies .

Keywords: Adult, Attention deficit disorder with hyperactivity, Methylphenidate, Selegiline,

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Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental disorders in childhood. It affects 3-6% of school-age children (1, 2). Some recent evaluations report the prevalence of 5.3% in childhood (3). The disorder is characterized by symptoms of hyperactivity, impulsivity and inattention. ADHD continues into adolescence and adulthood without treatment in about 60% of the cases. Therefore, the prevalence of the disorder among adults is at least 1-3% (4). Even some studies report the prevalence to be 1.2-7.3%. The estimated prevalence of DSM-IV adult ADHD over ten countries around the world was 3.4%. Prevalence estimates were significantly higher than this average in France (7.3%), U.S (5.2%) and Netherlands (5%); and significantly lower in Colombia (1.9%), Lebanon (1.8%), Mexico (1.9%) and Spain (1.2%) (5).

The following disabilities were found in 30-day functioning associated with adult attention-deficit hyperactivity disorder disability in: self-care, mobility

and cognition. The clinical presentation of ADHD often changes with increase in age as the patient moves from childhood to adulthood. The symptoms of inattention and impulsivity are more likely to persist into adulthood than symptoms of hyperactivity. The diagnosis of ADHD in adults might be debatable because before the publication of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the disorder seemed to apply only to children (6). In addition, the diagnosis of ADHD is dependent on the clinician's experience. Some physicians aren't still well-informed of the manifestations and importance of this disorder in adulthood.

Comorbidity is common among patients with ADHD. In children and especially in adolescents, comorbid disorders are often difficult to recognize ,but the existence of a comorbid condition is correlated with greater likelihood that the symptoms will persist into adulthood. In adults with ADHD, comorbidity of

several other psychiatric diagnoses is common and requires broader and more comprehensive treatment goals (7).

Diagnosis of adult ADHD is a longitudinal process requiring the documentation of ADHD symptoms with onset at not older than 7 years of age (pervasive as demonstrated in a variety of settings and severe enough to interfere with school) and occupation and social functioning. Adults must have childhood-onset and persistent current symptoms of ADHD to be diagnosed with the disorder. Adults with ADHD often present with marked inattention, distractibility, organization difficulties, and poor efficiency reflected in life histories of academic and occupational failures. (8)

Stimulants have been used in the treatment of childhood ADHD for 60 years and the efficacy of methylphenidate (MPH) in the treatment of adults with ADHD has been proven to be acceptable according to meta-analysis studies (9, 10). However, there are some concerns about stimulants. Up to 30% of those affected with ADHD may not respond to stimulants or may not be able to tolerate associated side effects such as appetite suppression, sleep disturbance, mood difficulties, or exacerbation of comorbid tic disorders (11).

A review of an article assessing the abuse potential of methylphenidate, states that the drug has a behavioral pharmacological profile similar to other abused stimulants. Overall 80% of the studies reviewed indicated that methylphenidate functions behaviorally in a manner similar to D-amphetamine or cocaine. It means that MPH produces comparable reinforcing, discriminative-stimulus, or subjective effects similar to those (12).

Some findings support a multisystem dysfunction underlying ADHD pathophysiology (13).

Selegiline is a type B monoamine oxidase inhibitor (MAOI), and by inhibiting the breakdown of dopamine and increasing synaptic dopamine levels it is expected to be beneficial in the treatment of ADHD (14). Selegiline is metabolized to amphetamine and methamphetamine, stimulant compounds that may be useful in the treatment of ADHD (15).

Selegiline produced dose-dependent changes in monoamine metabolites and DOPA plasma levels. Dopaminergic indices were associated with ADHD symptom severity and noradrenergic indices with persistence tasks (13).

Effects of chronic Selegiline administration on hyperactive behavior and brain monoamine levels have been studied in spontaneously hypertensive rats, and the results showed that selegiline could reduce hyperactivity and deficient sustained attention. The positive effect of selegiline on impulsiveness has been discussed to be due to either normalization of an asymmetric dopaminergic activity in the nucleus accumbens, or in a restoration of normal dopamine function in the prefrontal cortex (16).

Some clinical trials report the efficacy of Selegiline in child ADHD. One of them indicates that Selegiline

may target specific symptoms of ADHD including: sustained attention, the learning of novel information, hyperactivity, and peer interactions. Because this drug did not specifically reduce symptoms of impulsivity, Selegiline may be a preferred treatment for individuals who present with the primarily inattentive subtype of ADHD (17). Another study reports a significant improvement over the 60 days of treatment with Selegiline from the teachers' and parents' assessment scales (18). Treating child ADHD with Selegiline is as effective as methylphenidate with less side-effects of decreased appetite, difficulty falling asleep and headaches (17, 19).

However, it has been reported that Selegiline treatment is not more effective than placebo in adults (20).

Therefore, the authors designed this study to observe the efficacy of Selegiline in the treatment of adult ADHD.

Materials and Methods

Study Participants

The outpatient adults with ADHD were given CAARS self report screening form (Conners' Adult ADHD Rating Scale, 1999) and those with a high total score on the scale were interviewed by a psychiatrist (21). Interviewing with each one's partner helped to make the diagnosis more accurate. Those who met the DSM-IV diagnostic criteria for ADHD were placed for the recruitment procedure. Those who had been previously diagnosed with a psychiatric disorder were excluded. The exclusion criteria are as follows: suffering from a significant chronic medical disease like a history of seizures, a cerebra-vascular accident, a cardiovascular disease and current abuse or dependence on drugs within 6 months, pregnancy and breast-feeding. After a description of adult ADHD and the structure of the study, a consent form was obtained by each volunteer patient in order to consider the ethical standards of the Helsinki Declaration of 1975 revised in 2000. Eventually 28 men and 12 women aged 18-46 (mean 31.15 with SD of 7.046) completed the study procedure (22).

Study Design

The CAARS utilizes short, long, and screening self-report and observer rating scale forms. The instrument is designed for individuals aged 18 to 50 years and older. (21) The scales address ADHD symptoms as described in the Diagnostic and Statistical Manual Fourth Edition. This form had been translated to Farsi (Persian) and had been normalized by ICSS (Institute for Cognitive Science Studies in Tehran). Those with a total score of 30 and above were interviewed by a psychiatrist. Each one underwent a standard clinical assessment consisted of a psychiatric evaluation with a detailed history of childhood to consider WURS (Wender Utah Rating Scale, 1993), a structured diagnostic interview and a medical history. The partners of these probable patients with ADHD were

also questioned about the presence and severity of the symptoms as an observer's view.

Patients were randomized to receive Selegiline or methylphenidate in an equal ratio. The assignments were kept in sealed, opaque envelopes until the point of allocation. The randomization and allocation process were done by the secretary of the private clinic. Each patient was randomly assigned to receive treatment either with Selegiline (starting with 5mg/day to a maximum of 15mg/day) in group 1, or methylphenidate (starting with 10mg/day to a maximum of 40mg/day) in group 2 for an 8-week double-blind clinical trial. All the involved people in the study- the psychiatrist, the rater and the patients- were blind to assignments. Each patient filled CAARS self report screening form before starting to take medication and in weeks 2-4-6 and 8.

Patients were also assessed by a psychiatrist at the baseline and on each 14 days up to the 8 weeks period. Twenty patients refused to complete the study in each treatment group (ten from group 1 and ten from group 2). Their responses to the scale were unreliable as they consumed the medication irregularly. Therefore, 20 patients in each group completed the 8-weeks medical treatment.

Statistical Analysis

A two-way repeated measures analysis of variance (time- treatment interaction) was used; the two groups (Selegiline and methylphenidate) were considered as a between-subjects factor (group) and the scale total score (CAARS self report screening form) was used during the treatment as the within-subjects factor (time). In addition, a one-way repeated measures analysis of variance with a two-tailed post-hoc Tukey mean comparison test were performed on the change in CAARS self report screening form scores from the baseline.

Results were considered significant with $P \leq 0.05$. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. To consider, $\alpha=0.05$, $\beta=0.2$, the final difference between the two groups, at least score of 5 on the Teacher and Parent ADHD Rating Scale, $S=5$ and $power=0.8$, the sample size was calculated at least 15 in each group.

Results

There were no significant differences between the two groups in terms of gender, age, ethnicity and baseline score of CAARS self-report screening form.

The table demonstrates the data of those participants who completed the study procedure (Table 1).

The mean scores of the two groups are demonstrated in Fig. 1. There were no significant differences between the two groups at week 0 (baseline) on CAARS self-report screening mean score. Both groups showed a significant improvement over the 8 weeks of treatment and the trend seemed linear.

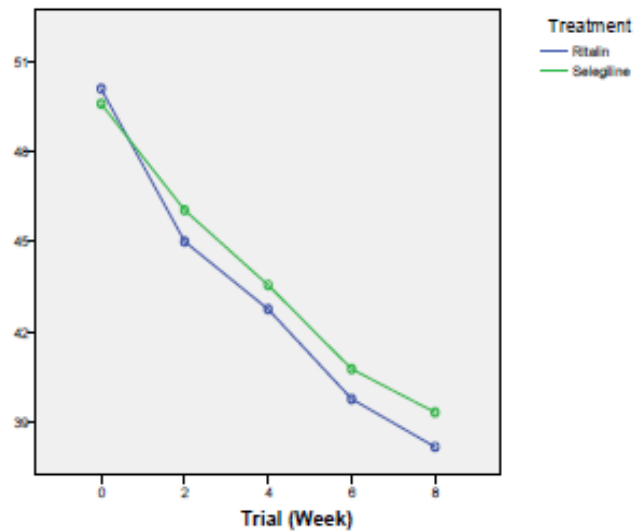


Fig. 1: Mean Scores of CAARS Self Report Screening Form Over 8 Weeks

Table1. Data of Participants

	Selegiline Group	Methylphenidate Group
Female	6	6
Male	14	14
Age (Mean + SD) (Year)	31.60 + 6.30	30.48 + 7.59
Baseline CAARS Score	49.60 + 5.39	50.10 + 5.66
Ethnicity	All Persian	All Persian

Table 2. Clinical Complications and Side Effects

Complications	Selegiline	Methylphenidate	P
Difficulty Falling Asleep	2	10	S
Increased Sleep	7	1	S
Abdominal Pain	3	4	NS
Headache	2	2	NS
Decreased Appetite	2	9	S
Nausea	3	4	NS
Irritability	1	3	NS
Anxiety, nervousness	2	4	NS
Dry mouth	3	3	NS

S=Significant, NS= Non-Significant

The difference between the two treatment strategies was not significant as indicated by the effect of groups, the between-subjects factor. The trend of treatment effect was the same in both groups over time.

A number of probable side effects were studied (Table 2). Nine side effects were observed over the trial all of which were mild and tolerable. In the frequency of side effects, the difference between the Selegiline and methylphenidate groups was not significant except for sleep pattern changes and decreased appetite. Decreased appetite and difficulty falling asleep were observed more frequently in the methylphenidate

group and increased sleep was observed more in the Selegiline group.

Discussion

In this double blind, randomized, controlled study of adults with ADHD, we found a statistically significant effect of Selegiline and methylphenidate for treatment of ADHD. No significant differences were observed between the two groups on the Conners' Rating Scale scores. This finding is in agreement with some previous studies that have indicated a positive effect of selegiline in the treatment of ADHD. As suppression of appetite and difficulty falling asleep were reported less in the Selegiline group, Selegiline can be a considerable therapeutic agent for patients facing these problems on MPH.

For many years, methylphenidate (MPH) has been one of the first-line treatments for attention-deficit/hyperactivity disorder. As some children with ADHD didn't respond adequately to stimulants and some encountered serious problems like deleterious reduction in their appetite, the need for finding a non-stimulant medication emerged. Moreover, prescribing a stimulant agent in patients with comorbid disorders such as tic disorder is not acceptable (23). The short half-life of MPH was also a reason of some discontent with the drug especially from a parental view.

Managing adult ADHD with psychotherapy seems more effective than child ADHD (23). However, many of adult sufferers need a medication. The literature supports the efficacy of MPH for treatment of adult ADHD (10, 24-27). Nevertheless, we encountered all the defects of stimulants mentioned about child ADHD in the adult form of the disorder. In addition, there is a serious concern about behavioral pharmacological profile of MPH since it functions in a manner similar to D-amphetamine or cocaine and has abuse and dependency potential like other psycho-stimulants (12). (Atomoxetine, a non-stimulant agent, is known as a pharmacological intervention for children aged 6 years and over with ADHD (28). There are also some evidence supporting the efficacy of bupropion, clonidine, modafinil and tricyclic anti-depressants in treatment of ADHD (29-31).

As a multi-modal intervention is considered to be an optimum therapeutic approach for most of psychiatric disorders, having a variety of choices of medications is also advisable.

Limitations

The small number of participants (considering that diagnosing and obtaining the agreement and satisfaction of adults with ADHD is a difficult task) should be considered and therefore further research in this field is needed.

Conclusion

The results of this study should be considered preliminary, as some other researches reported little efficacy of Selegiline. Managing parents who have under-treatment ADHD children who themselves suffer

from ADHD seems easier than other adults with the disorder. It can be a useful hint for studies where objections of adults with ADHD halt any interventions.

Selegiline significantly improved symptoms of adult ADHD and was well tolerated by participants of this study. It is as effective as methylphenidate in the treatment of adults with ADHD. As Selegiline has anti depressive effects, it can especially be used in adults with ADHD who suffer from comorbidity of mood disorders.

Selegiline can be a good alternative medication for the treatment of ADHD.

Conflict of interest

None declared.

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