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ORIGINAL PAPER

Comparison between the Efficacies of Modafinil and Citalopram in the Treatment of Major Depression

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ABSTRACT

Introduction: *Antidepressants are the most common treatment for major depression. Also, psychotherapy is used for the treatment of depression. Tricyclic antidepressants are among the most frequently used medications to treat depression, with many known side effects. Therefore, checking and replacing other suitable drugs is essential in order to reduce side effects. Thus, the present study aimed to compare the efficacy of Modafinil and Citalopram in the treatment of patients with major depressive disorder.*

Method: *This interventional study was performed in 2019 on 30 people aged 18 to 65 years who had been diagnosed with a major depressive disorder based on DSM-5 criteria as well as the Hamilton Depression Rating Scale (HDRS), on which they got a score above 25. Subjects were randomly divided into two groups: the first group received Modafinil tablets (200 mg once daily, in the morning) and the second group Citalopram (20-40 mg/day). A Chi-square test was used to analyze the qualitative findings, and an independent t-test was used to compare quantitative data.*

Results: *The results showed that changes in HDRS score were significant over time ($P < 0.05$). The mean difference in HDRS scores was significant in all stages among the study subjects ($P < 0.05$). However, there were no significant differences in HDRS scores between groups in terms of gender, age, marital status, education, occupation, and economic status, either before treatment or three and six weeks after treatment.*

Conclusion: *This was the first comparative study of Modafinil and Citalopram efficacy in treating patients with major depressive disorder. Larger-scale, longer-term clinical trials, including long-term discontinuation trials and placebo-controlled parallel treatment studies, are further necessary. Also, a larger sample size with a placebo comparison is recommended.*

Keywords: major depressive disorder, Citalopram, Modafinil, Hamilton Depression Rating Scale.

INTRODUCTION

Depression is one of the most commonly occurring mental disorders in the classification of mood disorders. Mood disorders include a wide range of disorders, the prominent feature of which is the patient's mood disorder. They are divided into depressive disorders, bipolar disorders, and two etiological disorders (mood disorders caused by physical illnesses and mood disorders caused by substances) (1). According to the World Health Organization, depression is the second most common disease after cardiovascular disease. It is considered the num-

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ber one health problem globally and, as the mother of many diseases, it imposes many psychological, educational, and economic costs to both the patient and society; also, due to its overdevelopment, it is known as mental cold (2).

Depression has a lifetime prevalence of 15%, which may reach up to 25% in women. It is more common in single than married people and in persons who either do not have a close interpersonal relationship or are divorced (3). Studies show high rates of this disease in Iran (4-6). Also, 10-15% of patients with depression have suicidal ideation and commit suicide. So, an effective treatment for these patients is essential. There are different approaches to treat depression. However, in the psychiatric approach, pharmacotherapy is considered the front line of treatment for depression (1).

Both antidepressants and psychotherapy are used to treat major depression. Tricyclic antidepressants (TCAs) are among the most common drugs used to treat depression and have many well-known side effects, especially anticholinergic side effects, postural hypotension, sleep disorders, and sexual dysfunction (7). Selective serotonin reuptake inhibitors (SSRIs) are the most widely used type of antidepressants. Their mechanism is to increase serotonin levels in the brain. Unlike monoamine oxidase inhibitors (MAOIs) and TCAs, SSRIs do not significantly affect norepinephrine levels in the brain. In addition, SSRIs have milder side effects and drug interactions, and their overdose in suicide attempts is less likely to cause death when compared to TCAs. Selective serotonin reuptake inhibitors cause headache and dose-related nausea, vomiting, and diarrhea. Insomnia, restlessness, and confusion that decrease over time have also been linked to SSRI use. Also, SSRIs have been linked to sexual dysfunction as well as weight loss/gain over time. Patients may lose weight at first but regain weight quickly. When SSRIs are combined with other drugs that increase brain serotonin levels, such as MAOIs, TCAs, sumatriptan (or Imitrex), linezolid (or Zyvox), tramadol (or Ultram), meperidine (or Demerol), they may cause confusion, high blood pressure, tremor, hyperactivity, coma, and even death (8). Therefore, checking and replacing another suitable drug is essential, considering the stated side effects.

Modafinil acts on dopamine, norepinephrine, serotonin, histamine, glutamate and gamma-aminobutyric acid (GABA) as a nervous system stimulant to reduce drowsiness, increase alertness and improve concentration and richness of thought and perception. It has also been suggested that the drug may reduce impulsivity. Modafinil was first approved by the Food and Drug Administration (FDA), in 1998, for sleep disorders (narcolepsy) and daily drowsiness in people with obstructive sleep apnea (3). It has been tested for efficacy as a booster agent for residual depressive symptoms such as fatigue and drowsiness (9). Although its mechanism is not fully understood, Modafinil appears to alter the balance of GABA and glutamate and activate the hypothalamus (8-11). Also, it increases metabolism in the central thalamus, central amygdala, and hippocampus.

Several open trials have shown that Modafinil improved persistent fatigue and daytime drowsiness in patients with major depressive disorder (MDD) (12, 13). In addition, three placebo-controlled trials examined the clinical effects of Modafinil in major depression (14-16). However, their results have not been consistent. Unlike classical stimulants such as amphetamines and methylphenidate, Modafinil is not significantly abused and is therefore important in treating patients with both depression and substance abuse (17). Considering the above mentioned issues on Modafinil benefits for depression, and given that no research has been done in Iran on its therapeutic effects in patients with depression, and also reminding that lack of both proper treatment of depression and drug tolerance by the patient causes hospitalization and imposes exorbitant costs on families, finding an effective treatment to control depression faster and better, with fewer complications and higher efficiency, is very important. So, the present study aimed to compare the therapeutic effects of Modafinil and Citalopram.

METHOD

Study population

The study population included patients aged 18 to 65 years, regardless of gender, who were diagnosed with MDD based on DSM-5 criteria. According to a similar study, in which the score of Hamilton questionnaire in both the treatment and control groups was reported at the end of the study (the sixth week), the sample size required to

compare the two groups with power 90, $\alpha = 0.05$, and $\beta = 0.1$ was calculated using Pass11 software in each group of 15 subjects.

The present study was a three-blind randomized clinical trial. After obtaining each participant's written consent and explaining the study conditions, patients were asked to complete a demographic questionnaire regarding age, gender, education, and economic status. Afterwards, a psychiatrist or psychiatric assistant examined all patients. The diagnosis of MDD was based on DSM-5 criteria (SCID-5) as well as Hamilton questionnaires which were randomly assigned to both study groups.

The first group received Modafinil tablets 200 mg day in the morning, and the second group Citalopram 40-40 mg day. Titration of both drugs was done gradually as follows: Modafinil 100 mg in the first week and 200 mg (two 100 mg tablets) in the second week, and Citalopram 20 mg in the first week and 40 mg (two 20 mg tablets) in the second week. Patients were grouped according to the Balanced Block Randomization method in groups A and B. The two study antidepressants were in boxes A and B, and only the study physician (supervisor) was aware of the drug content of each group. The control group (Citalopram) contained the relevant tablets, and in the intervention group, Modafinil tablets were prescribed to patients. Then, the supervisor did the numbering and recorded it in a notebook for each patient – for example, patient number 1 of drug A and patient number 2 of drug B or *vice versa*. Blinding is described below.

Inclusion and exclusion criteria

Inclusion criteria included age between 18 and 65 years, initial clinical diagnosis of major depression based on DSM-5 criteria (SCID-5), patient's or his/her guardian's written consent for participation in the research, ability to take the medication, and having a HDRS score over 25.

Exclusion criteria were as follows: depression due to physical illness or drug and substance use, presence of other psychiatric disorders according to DSM-5 criteria (SCID-5), presence of any severe or chronic physical illness (brain, heart disease), including vascular disease, seizures or history of substance abuse; history of gastric ulcer, pregnancy, alcohol and substance abuse during the six months prior to study, mania, IQ, psychosis, lactation, high severity of depression such as melancholic and suicidal ideation, history of receiving antidepressant in two to four weeks before starting the study (for example, MAOIs in the last four weeks but SSRIs or mirtazapine or SNRIs in the last two weeks), history of non-response or shift with the studied drugs, history of receiving lithium, lamotrigine, sodium valproate, atypical antipsychotics available other than ziprasidone and aripiprazole in the past two weeks or one month (depending on half-life or similar studies), being treated with Ritalin for any reason (15), presence of mixed symptoms in the recent episode (16), and presence of anxiety disorder, especially panic.

Blinding

The study physician (supervisor) administered pre-determined medication packages to all patients. Drug packages were completely similar in shape, and both the patient and project manager were not aware of their content. In addition, data collection, patient assessment, and form completion were done by the project manager and his assistant, who were both blinded to the content of the packages. Analysis was performed by the project consultant and the project manager, who were not aware of the content of drug packages, and only the patient group (group 1 or 2) was identified for data analysis. Therefore, the study was three-blind, and the content of the two drug groups was blinded from the stage of patients' entry into the study to that of data collection and analysis.

Randomization

Simple randomization does not guarantee a balance in the numbers of the study. In particular, if patients' characteristics change over time (for example, a patient's condition worsen before treatment completion), the imbalance cannot be early corrected. Block randomization is used to solve this problem. The main idea of patients' randomization is to divide the block into M blocks of size 2N, so that in each block, N patients are assigned A, and N patients are assigned B. The block is then randomly selected. This method ensures an equal treatment allocation block as long as the block is fully utilized. For example, in two therapies, A and B, the block size is $2 \times 2 = 4$. The therapeutic allocation may be within each block: 1) AABB, 2) BBAA, 3) ABAB, 4) BABA, 5) ABBA, and 6) BAAB. Depending on the number of treat-

ments, the block size should be short enough to prevent imbalance and large enough to prevent guessing treatment allocation in each group. The size of the block should be at least twice the number of treatment nodes – in our study it is not stated, so researchers are blinded to it. If blocks are expressed, treatment series in each block can be guessed (for example, in block 2N = 4, A A B must be B, and in A A B can be inferred), which can lead to selection bias.

Solutions to avoid such errors are non-disclosure of block mechanisms and using random block size.

In the third and sixth weeks of treatment, patients were re-visited, and the severity of the disorder was assessed via HDRS. In both groups, patients received drugs in the same way and on the same days. All members of the research team as well as all patients and their families were unaware of each treatment group design.

Data collection

Hamilton Depression Questionnaire for Depression

Hamilton Depression Rating Scale (HAM-D) is a multidimensional scale, which means that the specific scores of each item cannot predict the overall score of the scale. Several studies have examined the internal reliability of different versions of HAM-D and have shown results ranging from 0.48 to 0.92. Recent studies have obtained an internal reliability coefficient of 0.83 for HAM-D-17 and 0.88 for HAM-D-24.

Hamilton Depression Rating Scale is one of the first scales designed for the assessment of depression. It is used by the therapist who aims to find the severity of depression in the examined patient. The original version of HAM-D consisted of 21 items. However, Hamilton believed that the final four items (daily changes, paranoid symptoms, obsessive-compulsive symptoms) should not be included in the overall score, as these symptoms are either unusual or reflective and do not cause severe depression; thus, the 17-item version of HAM-D became the standard for clinical trials, and over the years it has been the most widely used scale in controlled clinical trials of depression. The scale has 17 questions: depression mode, guilt, suicidal ideation, insomnia (early, mid and late-night), measures of daily activity, psychomotor retardation, agitation, anxiety, etc. All questions will have a score between 0 and 4. According to this questionnaire, a score less than 7 indicates a response to treatment (18). This questionnaire was examined before the third and sixth weeks of the study. In Iran, the validity of this tool through correlation with Beck Depression Scale and dysfunctional attitudes scale have been reported as 0.55 and 0.39, and reliability between evaluators as 0.95 (19).

Structured clinical interview (SCI) for DSM-5 disorders (SCID-5)

Semi-structured interviews are used for primary DSM-5 diagnoses by a trained clinician or a mental health professional who is familiar with the diagnostic and classification criteria for disorders in the DSM-5. The validity and reliability of the Persian version of this questionnaire has also been investigated in Iran. The study of Sharifi *et a* examined the reliability and feasibility of the Persian version of the structured interview (SCID). The diagnostic agreed that the most specific and general diagnoses were moderate to good (kappa above 0.6). The overall agreement (total kappa) for the total current diagnoses was 0.52, and the total lifetime diagnoses was 0.55 (20, 21). SCID-PD (formerly SCID-II) is used to assess DSM-5 personality disorders. SCID-5 mood disorders, psychiatric disorders, substance abuse disorders, anxiety disorders, obsessive-compulsive disorder, and other related disorders like eating disorders, symptomatic disorders, some sleep disorders (*e.g.*, insomnia and excessive sleep disorders), intermittent disorder blast assesses gambling disorder, hyperactivity disorder, attention deficit disorder in adults, and trauma and stress disorders. SCID-5 has been published in various forms, including a prescription for physicians (SCID-CV) and a prescription for clinical trials (SCID-CT) (22).

Statistical analysis

All patient information, including demographic factors and clinical signs, were recorded in a checklist and entered into 22PSPSS software. Statistical analyses were presented in a descriptive section, which described the frequency of response to treatment as the primary variable, with all patients' demographic and clinical properties being reported based on descriptive criteria, and an analytical section, which included the establishment of statistical assumptions and proportional and non-parametric tests. A Chi-square test was used to analyze the qualitative findings, and an independent t-test was used to compare quantitative data. Mann-Whitney

parametric bread was used if the initial assumptions were not met as normal. All tests were evaluated at an error level of 5%.

RESULTS

The present study included a total number of 30 participants with a mean age of 35.40±7.47 years; 15 (50%) of them were males and 15 (50%) females. Out of all subjects, 17 (56.7%) were married and 13 (43.3%) single. The majority of participants had a higher education level, with 19 (63.3%) having master's and doctorate degrees. Fifteen (50%) subjects were government employees and 23 (76.7%) participants had incomes of over three million tomans month.

Study subjects had a mean HDRS score of 34.50±3.93 before the trial commencement, 28.10±4.63 after three weeks and 22.07±4.89 after six weeks from the start of the study. The trend of score changes was compared with repeated measure test, as shown in Figure 1.

The results revealed a significant difference between the mean HDRS scores within the group (before the intervention as well as three and six weeks after treatment) in all stages for both groups ($p < 0.05$).

The mean HDRS score in the study groups before the intervention as well as three and six weeks after treatment was evaluated according to each participant's education, occupation, economic status, and marital status. The results are summarised in Table 1.

DISCUSSION

The present study aimed to compare the efficacy of Modafinil and Citalopram for the treatment of patients with MDD. Subjects had a mean HDRS score of 28.10±4.63 during the intervals before treatment, 34.50±3.93 three weeks after treatment, and 22.07±4.89 six weeks after treatment. We found that the HDRS score in our patients was not significantly different between the two study groups, including Citalopram and Modafinil administration before treatment as well as three and six weeks after treatment. Also, it was shown that changes in HDRS score were significant over time ($P < 0.05$). However, there was no significant difference between the changes in HDRS score between the two groups in different periods. In all stages there was a significant mean

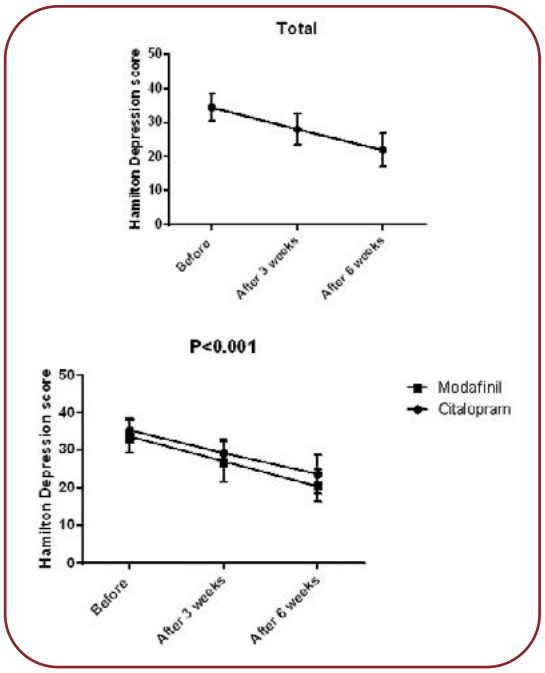

FIGURE 1. Mean and standard deviation of Hamilton depression score in general and by study groups in particular

difference (before the intervention as well as three and six weeks after treatment) between subjects' HDRS scores ($P < 0.05$). In addition, HDRS scores in the study groups before treatment as well as three and six weeks after treatment did not differ significantly with age, education, occupation, and economic status.

A single-blind clinical trial comparing the effects of Citalopram and nortriptyline in older adults with MDD was conducted by Mokhber *et al* in 2007 (23); it was designed to compare the two drugs for the treatment of depression due to the sensitivity of choosing the appropriate drug for the elderly. Thus, seven patients aged over 60 and diagnosed with MDD based on DSM-IV-TR diagnostic criteria were selected to participate in the research. The effectiveness of treatment was defined according to changes in the HDRS test score after eight weeks. The results showed no statistically significant difference in any of the changes in HDRS score in weeks 2 and 4 in the two groups. Also, the HDRS score in the study groups during specific periods did not differ significantly with gender, age, and economic status (23). Mokhber's study is different from ours regarding the type of drug used for treatment and the study population. Overall, the authors of the above mentioned study found that both drugs effectively reduced depres-

TABLE 1. Mean and standard deviation of Hamilton depression score in the studied groups according to demographic variables

Group	Citalopram			Modafinil			
Variables	**Before**	**After three weeks**	**After six weeks**	**Before**	**After three weeks**	**After six weeks**	**P-value***
Gender							
Male	36.22±2.53	29.77±3.83	23.22±5.49	35.83±4.53	28.16±5.03	20.0±4.04	0.830
Female	34.0±3.84	28.33±3.50	24.16±4.79	32.22±4.08	26.22±5.69	20.88±4.72	
P-value**	0.198	0.473	0.738	0.132	0.510	0.713	
Marital status							
Single	33.80±3.11	27.00±3.74	19.60±3.91	34.25±4.89	28.50±5.65	21.75±4.33	**0.035**
Couple	36.10±3.10	30.30±3.23	25.60±4.45	33.00±4.28	25.28±4.78	19.14±4.22	
P-value**	0.200	0.100	**0.024**	0.610	0.260	0.261	
Education status							
High school	38.00±0.00	32.00±0.00	25.00±0.00	-	-	-	0.465
Bachelor	35.16±2.85	29.00±4.51	23.50±6.65	32.00±3.82	26.00±4.69	18.00±2.82	
Masters and PhD	35.12±3.68	29.00±3.29	23.50±4.40	34.27±4.73	27.36±5.73	21.45±4.52	
P-value**	0.720	0.758	0.965	0.407	0.679	0.182	
Job status							
Government's employee	32.50±4.27	30.50±4.43	26.00±5.47	33.18±4.62	27.45±5.52	21.09±4.06	0.757
Non-governmental employee	36.00±3.11	30.00±3.11	24.50±4.34	33.25±4.78	27.00±5.34	19.00±5.35	
Unemployed	34.00±2.82	26.00±0.00	18.50±3.53	-	-	-	
Freelance	33.00±0.00	24.00±0.00	17.00±0.00	-	-	-	
P-value**	0.788	0.221	0.179	0.838	0.604	0.430	
Economic status							
2-3 M	33.50±6.36	28.00±5.65	22.00±4.24	32.00±6.08	24.00±8.66	18.33±3.21	0.908
> 3 M	35.90±2.84	30.00±3.52	24.81±5.05	34.08±4.25	27.75±4.43	21.08±4.52	
Without income	34.00±2.82	26.00±0.00	18.50±3.53	-	-	-	
P-value**	0.542	0.344	0.254	0.494	0.295	0.345	

*P-value: result of repeated measure test; **P-value: result of independent sample T-test

sive symptoms in the elderly, and the HDRS test score in both groups was reduced by more than 50%, but no difference was observed between the two drugs in terms of effectiveness and generalized results to all patients. Suffice to say, major depression needs further study.

In 2017, Kaser *et a* evaluated the effects of Modafinil for the treatment of depression in 60 patients (24). Their study showed that the Modafinil group had a significant performance in the episodic memory and working memory tests, although the administered drug did not improve sustained planning and attention. Overall, Modafinil (200 mg) improved episodic memory and memory function of patients with depression and may also be used as a therapeutic agent to help improve depression in people with cognitive problems (24). The findings of these researchers were not in line with ours due to the lack of evaluation of Citalopram, which can be considered separately as a suggestion for future studies and compared with the control group.

The effects of Citalopram on depression using STAR*D-based care as a follow-up for clinical practice were assessed in 2006 by Madhukar *et al*. Their clinical study included outpatients with MDD who were treated in 23 psychiatric hospitals and 18 primary care centers. Subjects received flexible doses of Citalopram prescribed by physicians for up to 14 weeks (25). Their findings were in line with ours regarding data collection tools and lack of significance in gender, age, mari-

tal status, education, and occupation between groups. However, it should be noted that the study of Madhukar *et a* only included Citalopram, while ours has also examined the effect of Modafinil. Finally, Madhukar and colleagues found that the sample response and improvement rates were very generalizable with Axis I and Axis III comorbidities and very similar to those observed in eight-week efficacy trials. Systematic use of measurement-based care methods is easily implemented and may help achieve these results (25). Also, limitations of their study included the design of open therapy, the use of a single antidepressant drug (Citalopram), and lack of placebo control, which agreed with the studies of Khan *et al* (2002) (26) and Kobak *et al* (1999) (27). More studies with other antidepressants are needed to determine whether the current findings could be generalized to other drugs too.

In 2019, Kheirabadi *et al* compared the effectiveness of Citalopram and metacognitive intervention on the severity of depression in patients with MDD (28). Their results showed that both Citalopram pharmacotherapy and metacognitive intervention reduced the symptoms of major depression, and metacognitive intervention caused more cognitive-emotional regulation (28). Their findings are inconsistent with our data regarding the fact that Citalopram and Modafinil were not evaluated simultaneously. However, the study of Citalopram with Modafinil and metacognitive intervention can be considered in future studies. The findings of Kheirabadi *et al* were consistent with those of Reynolds *et al* (29) in showing that patients with major depression were more likely to use emotion regulation strategies at the end of a period of metacognitive therapy.

In 2013, Mokhber *et al* aimed to find out if Citalopram was effective for depression and cognitive status in patients with stroke. Their study findings showed that, in the Citalopram group, changes in the depression score at the beginning of the study and the end of the eighth week of treatment and the total score of dementia and brief mental status test were statistically significant. There was a significant difference in dementia test scores at both the beginning and end of the study in the Citalopram and non-depressed groups. There was no significant difference between the three groups in terms of age, sex, and level of education (30), which was in line with our results, but it should be considered that the study of Mokhber *et al* explored the effects of a single drug on depression and cognitive status in patients with stroke. Also, their study grouping contradicted our results, which may be worth exploring in future research focused on the effects of Citalopram and Modafinil in depression.

In 2006, Vaishnavi *et a* examined the effect of Modafinil in the treatment of atypical depression and its therapeutic effects in a double-blind placebo-controlled trial (31). They introduced Modafinil as both a new awakening agent and monotherapy for unusual depression. The researchers found that Modafinil significantly changed the symptoms of atypical depression from 34.8 to 9.7 during 12 weeks of treatment. However, they did not see any difference in terms of gender, race, marital status, and age between the study groups. Modafinil was well tolerated and it was associated with significant weight loss compared to placebo (31). The discrepancy between their study and ours could lie in the lack of comparison with Citalopram and patients' sex.

A limitation of our study is the small sample size. It is better to consider more people with this disease to achieve a better precision in future studies. Other limitations included the lack of a control group in comparing Modafinil and Citalopram, and the fact that we did not determine the severity of depression, so both issues can be considered in future studies aiming to better evaluate the effect of these two drugs in the treatment of patients with MDD.

CONCLUSION

The present research was the first comparative study of the efficacy of Modafinil and Citalopram for the treatment of patients with MDD. Larger-scale, longer-term clinical trials, including long-term discontinuation and placebo-controlled parallel treatment studies with larger sample sizes, are necessary to thoroughly evaluate this issue. ❑

Ethical Approval: this study was approved by The Ethics Committee of Ahvaz Jundishapur University of Medical Science (IR.AJUM.REC.1398.830).

Conflicts of interest: none declared

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