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Evaluation of the effect of Escitalopram vs. placebo on changing the temperament traits of neuroticism

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Abstract---Introduction: Neuroticism is a personality trait that is most related to the mental health challenges. Escitalopram is the selective serotonin reuptake inhibitors (SSRIS) that are usually used in the treatment of depression and anxiety disorders. The aim of this study was to evaluate the efficacy and safety of escitalopram on improving the temperament traits on the neurotic patients. Methods: In this randomized placebo controlled trial, 172 residents in three hospitals in Ahvaz, Iran were randomly assigned to receive escitalopram 20 mg/daily/ orally (No=86, 29.9 ± 6.4 years with a range of 20 to 48 years old) or placebo (N=86, 29.8±6.3 years, ranged 21-47 years old) for 4 weeks.. At the beginning of the treatment the neuroticism and deoression scores were measured using NEO-60 and HAM-D questionnaires, and the patients were re-evaluated every two weeks during the treatment. The changes of temperament traits of neuroticism and depression in the two groups were analyzed using

SPSS software. Results: Administration of escitalopram in the treatment group reduced the neuroticism score 5.84 % and 13.3% after 2 and 4 weeks, respectively, compared with placebo group ($P < 0.01$). The changes in neuroticism temperament traits were not significant in placebo group during 4 weeks ($P < 0.05$). The use of escitalopram at least for 2 weeks was significantly effective in improving the depressive state of patients compared to placebo ($P < 0.01$) slight decrease in libido (34.9%) and gastrointestinal problems (26.7%) were the side effects of escitalopram consumption. Conclusion: Escitalopram is effective in the neuroticism treatment and depression improvement, and has a good safety profile.

Keywords--*Escitalopram, Neuroticism, depression.*

Introduction

Neuroticism is one of the main characteristics that describes human personality and predicts mental and physical disorders (1, 2). Neuroticism is a long-term tendency to a negative emotional state or anxiety. Neuroticism is not a disease but a personality trait. People with neuroticism typically tend to have anxiety, depression, self-doubt, and other negative emotions (3). Most studies suggest that a combination of both pharmacological and psychological interventions is effective in treating mental disorders. Medication is one of the oldest treatments for mental health disorders. Although a wide range of drugs are used in mental disorders, selective serotonin reuptake inhibitors (SSRIs) are still the main group of drugs used in these disorders (4). SSRIs increase the amount of extracellular serotonin by preventing the rapid reabsorption of serotonin in Presynaptic part of neurons. As a result, the concentration of serotonin in the synaptic cleft increases and more serotonin is delivered to the postsynaptic receptors. SSRIs have little effect on other neurotransmitters, such norepinephrine and dopamine (5). SSRIs most commonly prescribed in the treatment of clinical depression. However, they are also used in other mental disorders such as social anxiety, panic disorders, obsessive-compulsive disorder, eating disorders, chronic pain and sometimes, post-traumatic stress disorder(6).

Escitalopram belongs to the group of SSRIs drugs that has a chemical structure unrelated to other SSRIs. It has the same therapeutic effect as other SSRIs, and has fewer side effects than older-generation antidepressants. Escitalopram is also the least expensive antidepressant available to date (7). Escitalopram is used by some physicians to treat the social anxiety, obsessive-compulsive, panic, post-traumatic stress disorders (8); but the effect of escitalopram on the neurotic patients recovery is not fully clear and few studies have been done in this field (9,11). Neuroticism disease has a significant effect on the development of psychiatric disorders and reduces quality of the patients' life, so modifying these traits can play a preventive role in mental disorders.

In the present study, the impact of escitalopram on the improvement of neuroticism symptoms and depression disorders in resident assistant was evaluated.

1. Methods

1.1. Patient selection

This randomized placebo controlled trial was done from 26 July to 6 September 2022 in Ahvaz, Iran. The residents of 3 hospitals (Golestan, Razi, and Imam Khomeini) were selected for this study. Inclusion criteria included the diagnosis of neuroticism traits according to NEO-60 questionnaire with the score above 24 and the age range of 24- 45 years old. Patients who were pregnant, or intended to be pregnant, breastfeeding women, the presence of psychiatric disorder based on GHQ questionnaire with score above 23, the previous history of intolerance to SSPI antidepressants, the patients with severe side effects of escitalopram, the patients with a history of a chronic disease such as; cardiovascular, seizures and the people with a history of drug abuse were excluded from the study. Informed consent was obtained from all research subjects. Finally, 172 patients were selected.

1.1. Study plan

The evaluation of neuroticism was done by performing an initial interview using NEO- 60 questionnaire at the beginning of the study (Baseline) and then subject entered the study after confirming the neuroticism traits and fulfilling the inclusion and exclusion criteria.

Individual's psychiatric disorder was evaluated using GHQ questionnaire. In this screening, those who had received the score above 23, were psychiatrically interviewed. If the participant in the psychiatric interview had one of the psychiatric disorders, he or she was excluded based on the DSM-5.

After the initial evaluation, all patients were randomly divided into two groups, treatment (N=86) and placebo (N=86) according to the computerized randomized program. Escitalopram was initially administered at a dose of 5 mg / daily/ p.o for 5 days, and if tolerance was observed, the dose was increased to 20 mg / daily and continued for 4 weeks. The other group received the placebo. In treatment group, all patients received a dose of 20mg / daily during 4 successive weeks and no patient was excluded due to drug intolerance. The participants were blind to the treatment method and the used medication.

In both groups, neuroticism temperament traits were evaluated using NEO-60 questionnaire and the depression was measured using HAM-D scale. The treatment outcome and its safety were evaluated online, once every 2 weeks during the treatment period at <https://survey.Porsline.ir> site. The participants were blind to the treatment method.

In the first week of taking the drugs, all people were told to take half a pill and after a week to take the whole pill.

1.2. Measuring tools

NEO-60 Questionnaire: Five main personality factors of NEO questionnaire are neuroticism, extroversion, flexibility, agreeability and responsibility, which was set on the basis of Likert scale (completely disagree or completely agree) with the range of 0-4 (12). This questionnaire was performed by Mccary and Costa on 208 American students in a three month interval, which the validity coefficients were obtained between 0.75 to 0.83 (12).

HAM-D Questionnaire: HAM-D questionnaire provides a useful and precise screening tool for depressive symptoms in psychiatric patients (13). This questionnaire includes 21 items and has a score between 0-4. In this questionnaire, the score of 0-7 is considered as normal, 8-16 as mild depression, 17-23 as moderate depression and the scores above 24 indicate the severe depression. The reliability of this questionnaire has been proved in different studies (14, 15). Moreover, a meta-analysis study showed that after treatment and in the reevaluation, HAM-D was more sensitive to change compared to Beck Depression questionnaire (16).

1.3. Evaluation of results

In the treatment and placebo groups, NEO-60 and HAM-D scores were compared at the beginning of the study, at the end of the 2nd and 4th weeks of the treatment, to evaluate the result of the treatment and safety.

1.5. Ethics statement

The investigation was performed according to the Ethics Committee Guidelines of Ahvaz Jundishapur University of Medical Sciences (Ethic code: IR.AJUMS.HGOLESTAN.REC.1400.063).

1.4. Statistical Analysis

All analyses were performed using SPSS software version 22 (USA, IL, Chicago, SPSS Inc) for windows. In two groups, the comparison of the mean score of NEO60 and HAM-D components in the 2th and 4th weeks with the baseline was examined using student's t-test. $P < 0.05$ was considered significant in all tests.

2. Results

2.1. Demographic findings

A total of 172 patients (94 men (54.7%) and 78 women (46.3%)) was evaluated. The mean age of the patients in treatment group was 29.9 ± 6.4 year ranging 20-48 years old and in placebo group was 29.8 ± 6.3 year ranging 21-47 years old. In the treatment group, 46.5% were men and 53.3% were women, and in placebo group, 62.8% were men and 37.2% were women.

Effectiveness of escitalopram

Our findings indicated that treatment with escitalopram significantly reduces the neuroticism trait in the patients after 4 weeks ($P < 0.05$) (table 1). So that after 2 weeks of treatment, the rate of neuroticism trait reduction was 5.84% and after 4 weeks was 13.3% compared to the baseline (before intervention). The impact of escitalopram on extroversion, flexibility, agreeability, and responsibility traits was not significant ($P > 0.05$). During 4 weeks, no significant change was observed in any of the neuroticism components in the placebo group ($P > 0.05$).

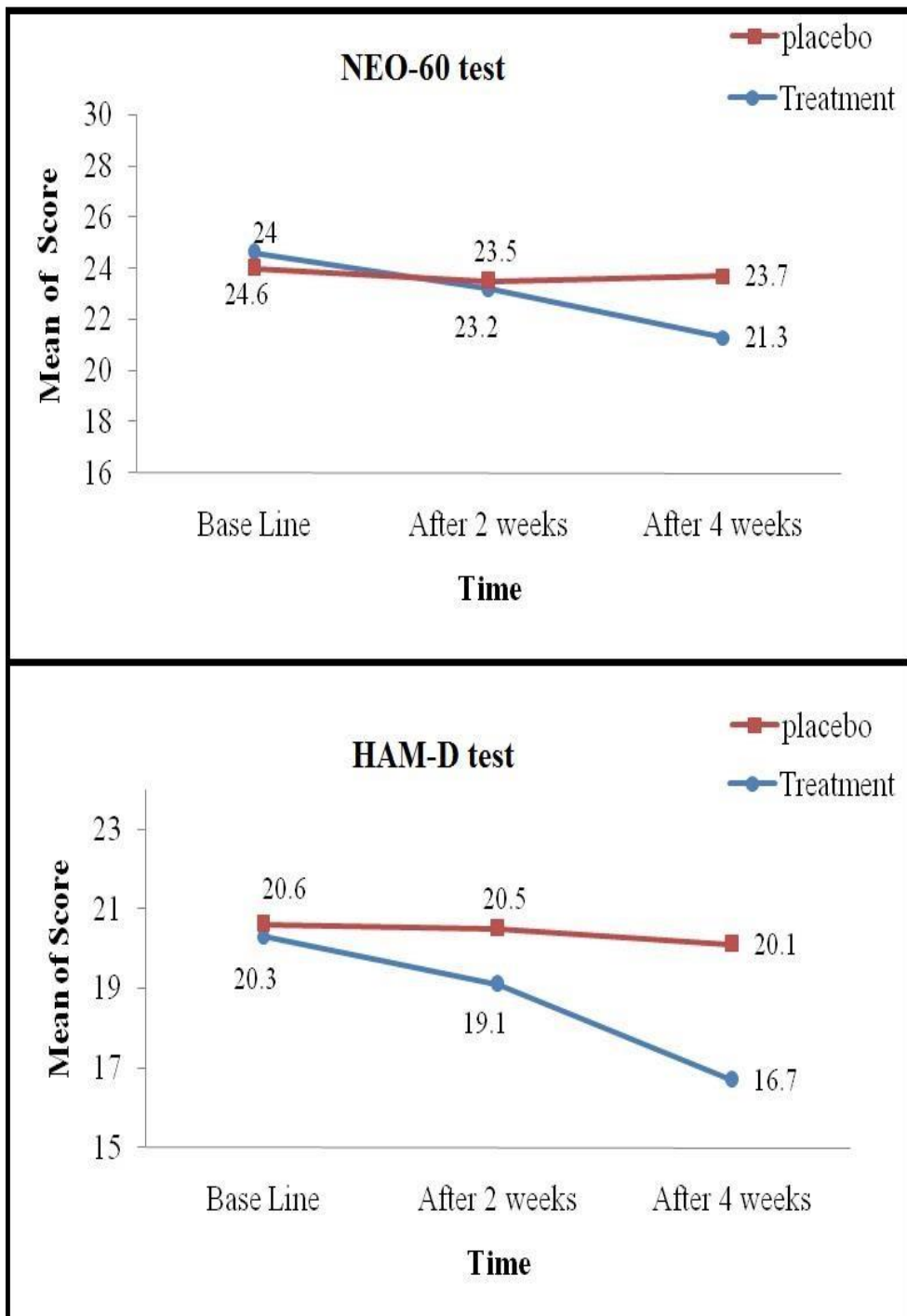
Table 1. Comparison of mean scores of neuroticism traits (NEO-60 test) in patients in the treatment group and placebo group in the 2nd and 4th weeks compared to baseline.

Group	components	Baseline (N=86)	2 nd Week (N=86)	Baseline V.S After 2 weeks		4 th Week (N=86)	Baseline V.S After 4 weeks	
				P Value	Changes (%)		P Value	Changes (%)
treatment	neuroticism	24.6±5.7	23.2±4.7	0.070	5.84	21.3±4.2	<0.0001	13.3
	extroversion	30.7±6.2	30.9±6.7	0.843	0.64	32.5±5.4	0.108	5.59
	flexibility	27.2±5.2	28.7±4.5	0.060	5.28	28.9±6.3	0.091	6.31
	agreement	28.9±6	29.3±5.3	0.679	1.24	30.3±5.2	0.126	4.70
	responsibility	33.4±4.3	33.8±4.2	0.562	1.14	34.4±3.9	0.094	2.92
placebo	neuroticism	24±4.8	23.5±4.8	0.519	1.98	23.7±5	0.711	1.16
	extroversion	30.6±4.3	30±6.4	0.489	1.89	31.1±6.1	0.587	1.44
	flexibility	28±6.3	29.3±6.5	0.192	4.60	29±4.5	0.238	3.56
	agreement	30±5.9	29.1±6.1	0.390	2.64	30.5±5.5	0.517	1.90
	responsibility	34.2±3.7	35.1±4.2	0.119	3.30	35±4.6	0.170	2.55

According to Table 2, the reduction in depression score in HAM-D test was significant after 2 weeks ($P = 0.09$) and 4 weeks ($P < 0.0001$) from the beginning of treatment in patients receiving escitalopram. The degree of depression in placebo group did not change significantly after 2 and 4 weeks.

Table 2. Comparison of mean score of depression (HAM-D test) in patients in the treatment and placebo groups in the 2nd and 4th weeks compared to baseline.

Group	Baseline (N=86)	Weeks2 (N=86)	Baseline V.S After 2 weeks		Weeks 4 (N=86)	Baseline V.S After 4 weeks	
			P Value	Relative reduction (%)		P Value	Relative reduction (%)
Treatment	18.3±2.8	17.1±3.3	0.009	6.85	14.6±3.7	<0.001	20.26
placebo	18.6±3.4	18.5±3.6	0.768	0.84	17.9±3.6	0.198	3.69



Picture 1. The trend of NEO-60 and HAM-D tests score in the neuroticism patients in the treatment and placebo groups for 4 weeks.

3.3. Adverse reactions to escitalopram

Evaluation the side effects of the drug in patients showed that taking escitalopram, especially at the beginning (first week) led to gastrointestinal complications (nausea, indigestion, constipation) in 26.7% of patients and decreased libido in 34.9% of them, which caused patients to complain, but they completed the course of treatment because escitalopram improved the neuroticism temperament traits.

Discussion

Although both pharmacological and psychological interventions are effective in treating mental disorders, but drugs therapy, especially selective serotonin reuptake inhibitors (SSRIs), remains a major treatment (17). Escitalopram is a member of the SSRIs family used to treat depression, anxiety and other disorders. In addition, this drug is used in some cases to treat obsessive-compulsive disorder, panic attack and Posttraumatic stress disorder(18). Escitalopram also has potential benefits, including the rapid onset of symptoms recovery and a low tendency for drug interactions.(19) . Review of previous research has shown that the effect of escitalopram on the temperament traits of neuroticism has been inconsistent in various studies. Moreover, considering that no similar study has been performed among the Iranian population, so in this study the effect of escitalopram versus placebo on the change of neurotic traits in 172 residents of Golestan, Razi and Imam Khomeini Hospitals in Ahvaz was investigated.

The results of the present study showed that taking 20 mg/daily of escitalopram has a significant impact on improving the temperament trait of neuroticism, and the highest effect was observed after 4 weeks. In this study, escitalopram reduced the neuroticism score by 5.84% after 2 weeks and by 13.3% after 4 weeks. The effect of escitalopram on other personality traits of neuroticism was not significant that could be due to the widespread and heterogeneous structure of neuroticism (10, 20) .

On the other hand, the people who were examined in our study had no psychiatric disorder based on GHQ questionnaire. Similar to our study, the effect of escitalopram on the improvement of neuroticism traits has been also reported in other studies. In a study conducted by Tse et al.,(2001) citalopram administration improved neuroticism in healthy participants without a family history of MD(11) .

In Knorr et al., study (2012) the impact of escitalopram on neuroticism traits was evaluated in 80 patients (both treatment and placebo groups) with first- degree relatives of MD and . They reported that administration of escitalopram at a dose of 10 mg/ daily for 4 weeks had a significant effect on improving neuroticism. Also, the greatest effect was seen on increasing patients' agreeability, but there was no significant difference in the traits of neuroticism, extraversion, flexibility and responsibility (9) . The reason for the difference in this study with our findings could be due to the difference in the dose of escitalopram, the severity of the disease, the sample size and the studeid population.

Evaluation the effect of escitalopram on depression showed that taking escitalopram for at least two weeks was significantly effective in improving patients' anxiety and depression compared with the placebo group. Escitalopram is widely used in the treatment of depression, and our findings have been proved by other researchers([21-24](#)).

In our study, it was observed that escitalopram has a significant effect on both neuroticism and the severity of depression in patients, which makes it difficult to distinguish the therapeutic effect on neuroticism from that on depression. Although the same finding has been also reported by Peters et al. (2019) ([10](#)) . The serotonergic neurotransmitter system is closely linked to depression and personality traits. Neuroticism, anxiety and depression are all linked to the serotonin system. According to the neuropsychological model of antidepressants, these drugs may modify the processing of emotions and thus make changes at the phenotypic level, such as symptoms and personality criteria ([12](#)) .

In the present study, the side effects of escitalopram were also investigated. No serious side effects were reported in escitalopram and placebo recipients during four weeks. However, sexual and gastrointestinal adverse effects were observed in patients using escitalopram. Other studies have reported insomnia and sexual dysfunction as side effects of taking escitalopram ([9](#), [25](#)) . Although the exact mechanism of sexual dysfunction due to SSRIs is not known, but a cumulative effect on various neurotransmission system (serotonergic, noradrenergic, dopaminergic, cholinergic, and nitric oxide) has been reported([26](#)) .

Limitations

This study has some limitations. Our findings show that the effect of escitalopram on personality traits is not the same. Therefore, certain personality traits can predict the escitalopram therapeutic response. The results of this study are preliminary and need to be repeated in a multicenter controlled therapeutic trial with a larger sample size. Considering that our sample consisted of non-clinical individuals with only neuroticism traits, so the results may not be generalized to of neuroticism populations with other psychiatric disorders (eg, higher levels of depression, bipolar disorder, drug abuser,...).

Conclusion

Our finding indicated that taking a doss of 20 mg/ daily escitalopram for 4 weeks is effective in improving the neuroticism trait and reducing depression. Given the significant effect of neuroticism in developing the psychiatric disorders and decreasing the quality of life, the use of escitalopram will be helpful in modulating the neuroticism traits and preventing the mental disorders in these patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

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