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Effectiveness of L-carnitine Supplementation to Sertraline for Treatment of Major Depressive Disorder: A Double-blind Randomized Placebo-controlled Trial

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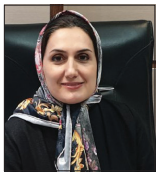

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ABSTRACT

Objectives: Despite the various treatment approaches proposed for major depressive disorder (MDD), the right treatment protocol for different patients is not the same. Supplementation of L-carnitine to antidepressants has been recommended in some studies; however, different results have been reported. This study aimed to evaluate the effectiveness of adding L-carnitine to sertraline in the treatment of patients diagnosed with MDD.

Material and Methods: This double-blind randomized controlled trial was conducted on 60 patients with MDD. The severity of the depressive disorder, as the primary research outcome, was assessed using the Beck depression inventory. The intervention group received 1000 mg of daily L-carnitine oral capsule along with 100 mg of sertraline; and the control group received a placebo (oral capsule containing 1000 mg of starch), along with 100 mg of sertraline every day. The primary outcome was assessed at baseline, the 3rd, and the 6th week.

Results: Although depression score decreased in both groups over time, the difference between the two groups was not significant ($P = 0.634$). Three patients reported adverse side effects; however, the difference between the two groups was not significant ($P = 0.554$).

Conclusion: Supplementation of L-carnitine to sertraline in patients with MDD did not show a significant effect on the improvement of depression severity.

Keywords: Major depressive disorder, Carnitine, Sertraline, Randomized controlled trial

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders that affect a large proportion of people, worldwide. A point prevalence of 12.9%, a 1-year prevalence of 7.2%, and a lifetime prevalence of 10.8% have been reported for this disorder and are significantly more prevalent in women than men.[1] Failure to treat this disorder causes psychological damage and many social and economic complications for patients.[2,3] Depression has been represented as the first ten leading causes of disability-adjusted life-years in the adult population (10–50 years) that imposes psychological, occupational, educational, and economic costs on the patient and societies.[4,5]

The previous studies revealed a considerable burden of this disease in Iran. A recent systematic review demonstrated depression as 35–45% of mental health problems in Iran which involves 8–20% of the total population in this country.[6]

Different approaches can be used to treat this disorder. Pharmacotherapy is considered as one of the first-line treatments for this disorder. Selective serotonin reuptake inhibitors (SSRIs) are reported as one of the most effective first-line drugs; although, finding proper treatments for patients, with higher effectiveness, fewer side effects, more patient adherence, and more economically affordable is an important field of psychiatric research.[7,8]

Several risk factors have been proposed for this disease. Some studies have suggested changes in the metabolism of fatty acids play an important role in the health of the nervous system. Given that carnitine can affect the function of the nervous system and neurotransmitter pathways, it has been shown that the concentration of this factor might be lower in patients with depression.[9] The function of carnitine as a transmitter of fatty acids through the inner membrane of the mitochondria for use in the process of oxidation, facilitating the reabsorption of acetyl CoA, increasing the production of acetylcholine, increasing the production of phospholipids in cell membrane, and preventing the death of neural cells is some of the proposed mechanisms.[9-12]

Although some evidence reported the role of L-carnitine as a safe and effective treatment for depressive disorders, the results of different studies are not the same.[13] This research was conducted to explore the effectiveness of L-carnitine as a complementary medication in the treatment of depression.

MATERIAL AND METHODS

Trial design

This double-blind randomized placebo-controlled trial was carried out on adult patients (aged 18 years and over) with a diagnosis of MDD referred to the medical centers of Babol University of Medical Sciences, during the year 2019–2020. The study participants were selected by convenience sampling.

Participants

The participants were adult persons with a diagnosis of MDD. The patient's diagnosis was performed through a clinical interview with a psychiatrist, based on the DSM-5 criteria.

Inclusion criteria

Age ≥18 years, diagnosis of MDD based on DSM-5 diagnostic criteria through a clinical interview with a psychiatrist was included in the study.

Exclusion criteria

The presence of serious somatic disorders, substance abuse except for cigarettes and caffeine, and history of high mood (mania or hypomania), mental dysfunction, dementia, acute psychiatric disorders according to the psychiatrist, and medication that causes depression in the patient were excluded from the study.

These individuals were allocated randomly into the intervention and control groups. Assignment of patients to the two mentioned groups was carried out using a simple random method (table of random numbers).

Interventions

All patients received 100 mg of sertraline (Tehran-Daru Pharmaceutical Company, Iran) daily along with either 1000 mg carnitine (Vana-Darougostar Pharmaceutical Company, Iran) or placebo (cooking starch), prepared in identical capsules.

Outcomes

Demographic characteristics including age, sex, marital status, level of education, occupation, and living location, in addition to the previous history of referral to a psychiatrist, and medical history of physical disorders were recorded in the research data sheets.

The participants' medical examination was performed at baseline, the 3rd and 6th weeks after the intervention.

The primary research outcome was the severity of depressive disorder which was assessed using the second version of the Beck Depression Inventory-II (BDI-II), and a 50% reduction of the baseline BDI score was considered as the treatment response.

The secondary research outcome was the side effects that the patients reported.

The BDI-II is a self-report questionnaire with 21 items that assess the person's feelings in the past 2 weeks. Each question has four options, and these options are scored on a scale of zero to three, respectively, and a higher score indicates the severity of depression. A score of 14–19 was defined as mild, 20–28 moderate, and 29–63 as severe depression.[14] The validity and reliability of the Persian translation of this questionnaire have been approved in previous studies.[15]

Sample size

With $\alpha = 0.05$, $\beta = 0.2$, $d = 0.8$, and 15% loss to follow-up, the sample size was calculated as 30 individuals for each case and control groups.

Allocation concealment mechanism

The statistical consultant of the project provided a random allocation sequence for assignment of the patients into the case and control groups. For concealment of the randomization process, a unique code was defined for each patient.

Blinding

Neither the assessor nor the patient knew the type of prescribed medications in the case and control groups. Only the research pharmacologist knew about the study groups that the patients were allocated. To reduce the related bias, all patients were interviewed in the 3rd and 6th weeks after the treatment by a psychiatrist who did not know the status of the patients in the two study groups.

Statistical methods

Data analysis was performed using the SPSS version 22 software package. A comparison of the research outcomes between the two groups was performed with *t*-test, Chi-square, and Fisher exact test. The severity of depressive disorder at baseline, the 3rd and 6th week, was assessed with repeated measure analysis.

To evaluate the effectiveness of L-carnitine on depression, the per-protocol (PP) and intention to treat (ITT) analyses were used. In PP analysis, the patients who completed the study until the end of treatment were included in the analysis process; however, in ITT analysis, all recruited patients in the study were included in the analysis. Missing items were replaced by multiple imputations and multivariate regression.

$P \leq 0.05$ was considered a significant level.

Registration

The trial protocol was registered on the Iranian website of clinical trials with approval number IRCT20150630022991N15. This protocol is available from: https://en.irct.ir/trial/54064.

RESULTS

Totally, 71 patients with MDD were assessed, and 60 persons (30 in the case group and 30 in the control group) were included in the research. The flow diagram of the participants is presented in [Figure 1]. In the case group, one patient needed to be hospitalized due to exacerbation of symptoms and was lost to follow-up. In the control group, two patients did not complete the treatment due to sertraline-related side effects and the patients' preference to discontinue the prescribed medication.

Mean age of the participants was 37.00 ± 9.71 (a range of 19–57) years; 25 individuals (41.7%) were male and 35 (58.3%) female. Mean age in the intervention group (38.13 ± 11.18) had no significant difference from the control group (35.87 ± 8.00) ($P = 0.371$). Baseline characteristics of the two study groups are presented in [Table 1].

This table shows that the case and control groups had no significant difference in demographic and medical characteristics ($P > 0.05$), except for the previous history of referral to a psychiatrist. In the case group, 33.3% of the patients reported a previous history of referral to a psychiatrist, while in the control group, this measure was 6.7% ($P = 0.010$). Before the intervention, 7 (11.7%) of the participants had mild, 22 (36.7%) moderate, and 31 (51.7%) had severe depression. Following the intervention, 14 (23.3%) had a normal condition, 13 (21.7%) mild, 19 (31.7%) moderate, and 11 (18.3%) had severe depression scale at the 3rd week of treatment. These values improved to 39 (65.0%) normal, 10 (16.7%) mild, 5 (8.3%) moderate, and 3 (5.0%) severe depression at the 6th week of the intervention.

The severity of depression at baseline, the 3rd and 6th weeks after the intervention is presented in [Table 2 and Figure 2]. This table and figure represent the improvement of the BDI score in each case and control group, over time; however, the difference between the two groups was not significant.

Both the patients who had a previous history of mental disorders and the individuals without this history showed a considerable improvement in BDI score, over time; however, the difference between the case and control groups was not significant. Among the patients with this previous history of psychiatric problems, the mean depression score in the case group decreased from 27.40 ± 8.31 at baseline to 17.80 ± 7.53 (at the 3rd week) and 11.90 ± 8.19 (at the 6th week); and in the control group, these measures decreased from 30.50 ± 14.85 to 24.50 ± 14.85 and 19.50 ± 14.85, respectively ($P = 0.388$). Among those patients who did not report previous mental disorders, the mean BDI score in the case group changed from 30.53 ± 9.64 to 20.42 ± 9.03 and 11.79 ± 7.47; and in the control group, these measures changed from 31.04 ± 8.05 to 21.08 ± 7.63 and 13.31 ± 5.05, respectively ($P = 0.687$).

Out of a total, 57 (95.0%) patients had no side effects; one patient in the case group, and two persons in the control group showed drug side effects ($P = 0.554$).

DISCUSSION

This randomized controlled trial showed no significant difference in the severity of depression (BDI score) between the patients with MDD who received sertraline supplemented with L-carnitine and those who received only sertraline.

A few similar trials can be found to explore the treatment impact of carnitine supplementation on depressive symptoms.[16] MahmoudianDehkordi *et al*. examined plasma samples from 136 patients with MDD 18–84 years of age who

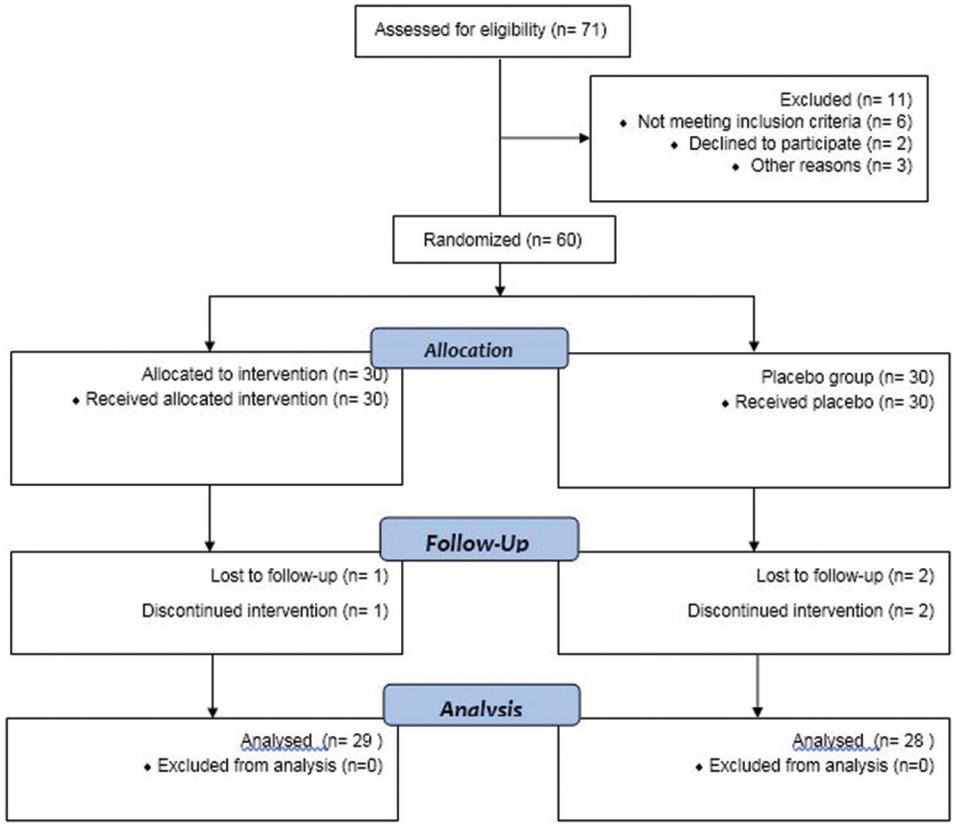

Figure 1: Flow diagram of the participants.

Table 1: Baseline characteristics of the two research groups.

Characteristics	Study group		Total *n* (%)	*P*-value (Chi-square)
	Intervention *n* (%)	Control *n* (%)		
Gender				0.432
Male	14 (46.7)	11 (36.7)	25 (41.7)	
Female	16 (53.3)	19 (63.3)	35 (58.3)	
Level of education				0.304
Up to high-school	15 (50.0)	7 (23.3)	22 (36.7)	
Diploma	7 (23.3)	17 (56.7)	24 (40.0)	
Academic education	8 (26.7)	6 (20.0)	14 (23.3)	
Marital status				0.739
Single	24 (80.0)	25 (83.3)	49 (81.7)	
Married	6 (20.0)	5 (16.7)	11 (18.3)	
Occupation				0.840
Housekeeper	10 (33.3)	12 (40.0)	22 (36.7)	
Employee	7 (23.3)	7 (23.3)	14 (23.3)	
Others	13 (43.3)	11 (36.7)	24 (40.0)	
Living location				0.787
Rural	10 (33.3)	11 (36.7)	21 (35.0)	
Urban	20 (66.7)	19 (63.3)	39 (65.0)	
Previous history of referral to a psychiatrist				0.010
No	20 (66.7)	28 (93.3)	48 (80.0)	
Yes	10 (33.3)	2 (6.7)	12 (20.0)	
Previous history of physical disorders				0.718
No	26 (86.7)	25 (83.3)	51 (85.0)	
Yes	4 (13.3)	5 (16.7)	9 (15.0)	

Table 2: Comparison of depression (BDI) score between the two study groups at baseline, the 3rd and 6th weeks after the intervention.

The type of analysis	Examination time	Intervention group Mean±SD	Control group Mean±SD	*P*-value
Per-Protocol analysis	At baseline	29.45±9.17	31.00±8.26	0.418
	The 3rd week	19.90±8.81	21.29±7.92	
	The 6th week	11.83±7.58	13.75±5.81	
Intention to treat analysis	At baseline	29.80±9.22	30.63±8.10	0.634
	The 3rd week	20.29±8.93	20.84±7.89	
	The 6th week	11.98±7.50	13.37±5.90	

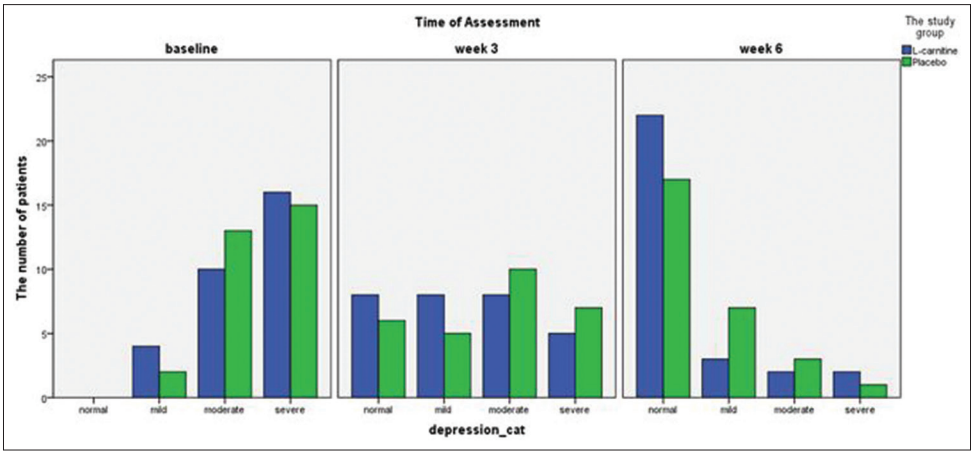

Figure 2: Categorization of depression (BDI) score in the two study groups at baseline, the 3rd and 6th weeks after the intervention.

were receiving antidepressant medications. After 8 weeks of SSRI treatment, the plasma concentration of several metabolites from different classes changed significantly, for example, among the acylcarnitines, an increased level of three short-chain acylcarnitines, and a decrease in medium and long-chain acylcarnitines were observed; and they suggested the effect of acylcarnitine metabolism on β-oxidation in SSRI treatment response.[11] Veronese *et al*. conducted a systematic review and meta-analysis to investigate the impact of acetyl-L-carnitine (ALC) on depressive symptoms. They found 12 randomized controlled trials with a total of 791 participants and reported a significant effect of ALC on the reduction of depressive symptoms, even, in three trials comparing ALC versus antidepressants, ALC demonstrated similar effectiveness compared with established antidepressants in reducing depressive symptoms. Furthermore, they reported a lower incidence of adverse effects in the ALC group compared with the antidepressant group.[16] This difference in results might be due to the study design, difference in the conducted intervention, and the sample size.

ALC, an acetyl ester of carnitine, is an endogenous molecule with biological and pharmacological activities in central and peripheral nervous systems and has a key role in neuronal metabolisms such as β-oxidation, glucose utilization, glycogen production, and ammonia cycle; furthermore, exogenous ALC may increase the process of neurogenesis in prefrontal-limbic areas.[17] Although animal and cellular models suggest that ALCs on neurotransmitter regulation, improvement in dysfunctional neuroplastic changes, and membrane modulation may play important role in the treatment of depression, more controlled trial data with adequately-powered, well-designed, and advanced methodology should be performed to conclude whether ALC as a monotherapy or supplementation agent may be clinically beneficial for MDD.[9,18]

Although pharmacologic approaches are the most important treatment strategies for MDD, response rates to the first-line antidepressants are moderate and remission is observed in about 30–45% of patients. Some risk factors such as biopsychosocial characteristics, clinical features of the current depressive episode, and physical and mental comorbidities can have an impact on response to pharmacologic treatments.[19,20] Therefore, some recent evidence recommends individualized planning for patient treatment.[21]

Complementary and alternative or integrative medical treatments have been proposed as monotherapies or as add-on adjuncts to other treatment approaches in patients with mild-to-moderate MDD, and the literature review demonstrates a wide list of these complementary treatments.[22]

Our findings showed an improvement in depression scores at different time intervals in both groups. In other words, treatment with sertraline, regardless of supplementation with L-carnitine or without it reduced the severity of depression, over time. Furthermore, in this research, both groups showed a positive treatment response in the 3rd and 6th weeks after the initiation of the intervention. Chiechio *et al*. suggested that L-carnitine may exert a faster onset of antidepressant effect than that of conventional antidepressant drugs;[13] however, in our result, the difference between the two groups was not significant.

The two study groups showed no significant difference in side effects. This result indicates that the addition of L-carnitine to sertraline did not exacerbate treatment complications. Syncope, gastrointestinal side effects, dizziness, xerostomia, confusion, hallucinations, tremor, sexual dysfunction, and bleeding risk have been reported as adverse effects of the sertraline.[23] In this research, 95% of the participants had no unwanted side effects. Only two patients in the control group reported headache, insomnia and restlessness, and discontinued the study protocol.

The study design, as a double-blind randomized controlled trial, is the most important strong point of this research. The low sample size and lack of long-term follow-up of patients can be reported as the limitations of this study. A large multicenter controlled trial is recommended for future studies to evaluate the effectiveness of L-carnitine alone or supplemented with different antidepressants in the treatment of patients with MDD.

CONCLUSION

Supplementation of L-carnitine to sertraline in patients with MDD did not show a significant effect on the improvement of depression severity.

Acknowledgment

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Authors' contributions

AR, FK, EZ, HS, and SM contributed to the conception and design, as well as the acquisition, analysis, and interpretation of data. SM drafted the article. All authors read the manuscript and approved the final version of the article to be published.

Ethics approval

This research has been approved by the Ethics Committee of Babol University of Medical Sciences, Iran, with identification ID: IR.MUBABOL.REC.1399.319.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

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Conflicts of interest

There are no conflicts of interest.

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