VOLUME LXXVI, ISSUE 1, JANUARY 2023

ISSN 0043-5147
E-ISSN 2719-342X

Wiadomości Lekarskie
Medical Advances

Official journal of Polish Medical Association has been published since 1928

INDEXED IN PUBMED/MEDLINE, SCOPUS, EMBASE, EBSCO, INDEX COPERNICUS,
POLISH MINISTRY OF EDUCATION AND SCIENCE, POLISH MEDICAL BIBLIOGRAPHY

ORIGINAL ARTICLE

SAFETY AND EFFICACY OF THE COMPLEX DEPRILIUM® IN REDUCING SUBCLINICAL SYMPTOMS OF DEPRESSION IN PATIENTS WITH CHRONIC NON-COMMUNICABLE DISEASES: DOUBLE-BLIND RANDOMIZED CONTROLLED STUDY

DOI: 10.36740/WLek202301119

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ABSTRACT

The aim: To evaluate the effectiveness of the use of the Deprilium® complex for the relief of subclinical symptoms of depression in patients with NCD.

Materials and methods: There were 140 patients involved in the study. To assess the subclinical symptoms, the Hamilton Depression Rating Scale (HAM-D) was used. In order to obtain additional information about the patient's condition, the Somatic Symptom Scale SSS-8 and the Quality of Life Scale (QOLS) were used. Patients were randomized by block randomization to an intervention group, which took Deprilium® complex, and a control group, which took placebo.

Results: After 60 days a statistically significant difference was observed in all clinical indicators between the intervention group and the control group. The median value of the HAM-D scale differed between the groups by 6 points, significantly ($p < 0.000$) lower results were observed in the intervention group, which participants were taking the Deprilium® complex. When comparing the indicators of the intervention group on the 1st and on the 60th day of the study, statistically significant changes ($p < 0.000$) were observed in all three indicators.

Conclusions: The received results confirm the available evidence for the properties of SAMe in depression and complement them with evidence of the effectiveness of the Deprilium® complex that contains SAMe and L-methylfolate with methylcobalamin, which together produce pharmacological and clinical synergy to reduce the severity of subclinical depressive manifestations in patients with NCD. Further studies of the effectiveness of the use of the Deprilium® complex in patients with NCD are required.

KEY WORDS: depression, chronic non-communicable diseases, S-adenosyl-L-methionine

Wiad Lek. 2023;76(1):136-144

INTRODUCTION

Non-communicable diseases are the leading cause of death worldwide: four main types of chronic non-communicable diseases (NCD) - cardiovascular disease, cancer, chronic obstructive pulmonary disease, diabetes - cause >2/3 of all deaths, making them a global problem [1]. Currently, in about half of the world's population at least one non-communicable disease is detected, and in 1/4 - more than one [2]. NCD such as cardiovascular disease, diabetes, cancer and chronic respiratory diseases are often accompanied by depressive manifestations, and this connection attracts increasing attention of researchers from around the world [3]. Depression is noted in such patients 2-4 times more often than in people without

NCD, and this combination creates a significant burden on health systems of middle- and low-income countries [4]. Presence of more than one chronic illness, female gender, poor education and lack of permanent relationships are associated with higher risks of developing depression [5]. In this regard, the World Health Organization recommends co-management of the patient with the NCD by an internist and a mental health professional [2-3]. Lack of comprehensive approach to the treatment of such patients can lead to lack of compliance, irrational double diagnostic testing, risks of incorrect interaction of pharmacological drugs, excessive burden on hospitals and even increased mortality [2]. The team approach is important for providing health services for patients with both non-communicable diseases and mental health problems [6].

Thus, there is a need to find approaches to the early therapy for depressive symptoms in patients with NCD, which would allow us to start managing the symptoms at the beginning of their occurrence. Existing approaches to early symptom management, despite their advantages, are still not widely available [6]. Therefore, the search for a therapy that is at the same time effective, safe and doesn't create an economic burden for patients, simple and clear -- this search is still relevant.

A promising candidate for such therapy may be the Deprilium® complex, which contains S-adenosyl-L-methionine (SAMe), L-methylfolate and methylcobalamin. It is a coenzyme that is naturally synthesized in the human body and participates in the construction of neurotransmitters and phospholipids in the brain; adding it to the diet increases the level of serotonin, dopamine and dilseril phosphate [10]. There are reports in the literature that SAMe levels are significantly lower in depressed patients than in people without depressive symptoms [6]. In this case, intravenous or oral administration of SAMe is associated with a significant increase in its levels in the cerebrospinal fluid, which indicates its ability to penetrate the blood-brain barrier. These observations provide a rational basis for the antidepressant effect of SAMe, which has been confirmed in several countries [7]. In a 2020 systematic review, the authors concluded that SAMe had a significantly greater effect on depressive symptoms than placebo, both as monotherapy and in combination with antidepressants, comparable to such widely used antidepressants as escitalopram and imipramine [9]. A large multicenter study found that taking SAMe at a dose of 400 mg per day was indeed associated with a significant reduction in the severity of depressive symptoms after 7 days, and the results kept improving after another 15 days [1]. SAMe has proven to be a quite safe substance, as most side effects are mild, clinically insignificant or transient [1, 7]. Combining SAMe with antidepressants improved their effect in patients with resistant depression and had no increased health risks, among the most common side effects were gastrointestinal disorders and headache [8].

SAMe synthesis is inseparably linked to the presence of folic acids and cobalamin [11] contained in the Deprilium® complex to create pharmacological and clinical synergism of action. This induces the interest to study the effectiveness of the use of the Deprilium® complex in subclinical depressive states in patients with NCD. However, its effect on subclinical manifestations of depression in such population is still insufficiently studied, which makes further research in this area relevant.

THE AIM

To evaluate the effectiveness of the use of the Deprilium® complex to relieve subclinical symptoms of depression in patients with NCD.

MATERIALS AND METHODS

Design of the study: double-blind randomized controlled trial with parallel groups.

On the basis of the Department of Medical Psychology, Psychosomatic Medicine and Psychotherapy of the O.O. Bohomolets National Medical University (monocentric study) in compliance with ethical and deontological norms in accordance with the principles set out in the Declaration of Helsinki, there were 140 patients involved in the study. Before taking part in the study, the participants reviewed the protocol and signed an informed consent.

Criteria for inclusion in the study: men and non-pregnant women who are not breastfeeding, aged 18-65 years; 0–14 points on the Hamilton Depression Rating Scale (HAM-D).

Non-admittance criteria: participation in a study during 1 month before the screening; a mental disorder diagnosis; a traumatic brain injury or a stroke in anamnesis; taking antidepressants ≤1 month before the involvement in the study.

ENDPOINTS

The primary endpoints were the total score on the Hamilton Depression Scale (HAM-D). Secondary endpoints - the total score on the scale of somatic symptoms (Somatic Symptom Scale - SSS-8) and the Quality of Life Scale by O. S. Chaban (Quality of Life Scale - QOLS).

PSYCHODIAGNOSTIC TOOLS

The HAM-D scale was used to assess subclinical symptoms. SSS-8 and QOLS were used to obtain additional information about the patient's condition.

The 17-item Hamilton Depression Rating Scale (HAM-D) consists of 17 items (9 of which are rated from 0 to 4 points, and 8 from 0 to 2 points) filled out by a specialist during a structured clinical interview [12]. Interpretation of the final score in this study was carried out in accordance with the updated in 2019 recommendations of the National Institute for Health and Awareness Institute for Health and Care Excellence (NICE) on therapy and management of depression in adults, where 0–7 points - stand for no depression, 8–13 - subclinical manifestations, 14–18 - moderate manifestations, 19–22 - moderate severity, ≥23 points - severe manifestations of depression [13].

The Somatic Symptom Scale (SSS-8) is a brief self-questionnaire of the somatic manifestations of depression developed by Gierk B. et al. [14], which consists of 8 questions, each rated within 0-4 points, where 0 -"Did not bother at all", 4 - "Bothered a lot". Assessment of somatic symptoms occurs by calculating the total result, which can vary between 0-32 points. The results are interpreted as follows: 0-3 points - minimal, 4-7 - low,

8–11 - medium, 12–15 - high, 16–32 - very high degree of intensity of somatic symptoms [15].

Chaban A.S. Quality of Life Scale (CQLS) is a questionnaire designed to assess the quality of life, containing 10 questions on different aspects of the life of the subject. It is necessary to indicate the number of points that is most suitable, from 0 ("Not at all satisfied" to 10 ("Extremely satisfied"). Assessment of the quality of life occurs by calculating the total score, which can vary from 0 to 100. A score of up to 56 points corresponds to an extremely low level of quality of life, from 57 to 66 – low, 67–75 points correspond to an average level, 76–82 points – high, from 83 points – a very high level of quality of life [16].

PROTOCOL AND DESIGN

The research was conducted on the basis of the Department of Medical Psychology, Psychosomatic Medicine and Psychotherapy of the O.O. Bohomolets National Medical University. Having received information about the study and having given written informed consent, and having undergone a screening procedure for eligibility, participants completed QOLS and SSS-8 questionnaires and were assessed at a structured clinical interview for depression (HAM-D), that met time point T1. Group formation was performed by block randomization to obtain equivalent groups. Patients were assigned to an intervention group that used Deprilium® twice per day (200 mg of S-adenosyl-L-methionine in the form of capsules (total dose of 400 mg / day) in combination with 0.4 mg of L-methylfolate and 0.25 mg of methylcobalamin), or to a control group that received placebo in a similar form and at a similar frequency for 60 days. After 60 days, a re-evaluation was performed on the scales HAM-D, SSS-8, QOLS, which corresponds to the time point T2.

CALCULATION OF THE SAMPLE SIZE

Taking that alpha is 0.05 and the sampling power is 80%, to track the difference between groups of 2 points on HAM-D, assuming a standard deviation is 4 and a dropout risk is equal to 10%, it was necessary to involve 70 people in each group.

STATISTICAL ANALYSIS

Qualitative data are presented through a number of observations and the percentage of the total number of observations. To assess the normalcy of distribution of quantitative indicators the Shapiro-Wilka criterion was used. Quantitative data are presented by mean and standard deviation (M ± SD), or by median and interquartile range [Med (IQR)], as appropriate. To assess the difference between two unrelated samples, the t-test for unrelated samples was used (in case of submission to the law of normal distribution). In the case of a distribution other than normal, to estimate the difference between two unrelated samples the U-test by Mann-Whitney for unrelated samples was used. To estimate the difference between two related samples, in the case of a normal distribution, the t-test for related samples was used, and in the case of a distribution other than normal, the Wilcoxon test for unrelated samples was used. Statistical data processing took place using the programming language R using the environment for statistical calculations EzR v1.54 [17]. Data visualization was performed using the Python programming language with the add-ons matplotlib and seaborn.

RESULTS

The average age of patients was 39.05 ± 9.92 years. 84 (60%) of the subjects were female, 56 (40%) - male. The majority (n = 103; 73.57%) of respondents at the time of participation in the study were married, a minority (n = 37; 26.43%) had no long-term partner.

Almost all the participants (n = 134; 95.71%) were employed and only a few (n = 6; 4.29%) were temporarily unemployed. Prior to randomization, the groups did not differ significantly according to any of the socio-demographic indicators (Table I).

79 (56.43%) participants had hypertension, 33 (23.57%) had bronchial asthma, 27 (19.29%) had diabetes, and 19 (13.57%) had chronic obstructive bronchitis. 122 (87.14%) had one NCD, 18 (12.86%) participants had two. No statistically significant differences in the structure of morbidity were found prior to randomization (Table II).

At the time of involvement in the study all participants (n = 140) noted subclinical depressive manifestations on the HAM-D scale. The mean value in the whole sample was 9.02 ± 0.93. According to the SSS-8 scale, the minimum level of somatic manifestations was observed in 12 (8.57%) participants, low - in 38 (27.14%), medium - in 51 (36.43%), high - in 36 (25.71%), very high - in 3 (2.14%) participants. According to the QOLS scale, the average value for the entire sample was 8.98 ± 3.75. It was found that 46 (32.86%) of the study participants have a very low level of quality of life, 37 – low (26.43%), medium - 34 (24.29%), high - 12 (8.57%), very high - 11 (7.86%). The average in the whole sample was 62.54 ± 14.70. Comparisons of the intervention group and the control group at the pre-randomization stage are presented in table III.

Table I. Social and demographic characteristics of the intervention and control groups

Variables	Intervention group (n=70)	Control group (n=70)	T / χ^2	p
Age	37.72 ± 10.50	40.37 ± 9.18	t = -1.58	0.115
Gender				
female	42 (60%)	42 (60%)	0	1
male	28 (40%)	28 (40%)		
Marital status				
married	52 (74%)	51 (73%)	0	1
single	18 (26%)	19 (27%)		
Employment status				
employed	68 (97%)	66 (94%)	0.174	0.676
unemployed	2 (3%)	4 (6%)		

Table II. Morbidity structure in the study participants

Illness	Intervention group (n=70)	Control group (n=70)	χ^2	p
Arterial hypertension	35 (50%)	44 (62%)	1.85	0.173
bronchial asthma	20 (28%)	13 (18%)	1.42	0.232
chronic obstructive bronchitis	9 (12%)	10 (14%)	0	1
diabetes	15 (21%)	12 (17%)	0.183	0.668

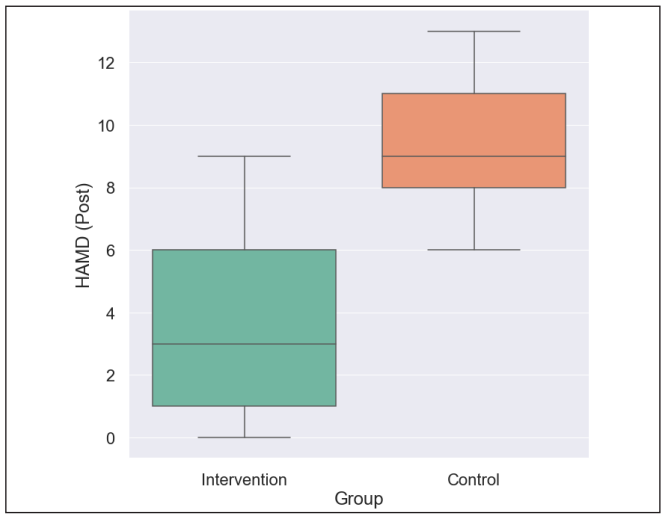

Fig. 1. Median values and interquartile range on a scale HAM-D in the control group and the intervention group

After 60 days (T2), a statistically significant difference was observed for all clinical indicators between the intervention group and the control group. The generalized results are presented in table IV.

The median value of the HAM-D scale differed between groups by 6 points, significantly ($p < 0.000$) lower results were observed in the intervention group which participants had been taking the Deprilium® complex during all that time (Fig. 1), which signaled about the lower degree of depression in this group.

There was also a difference observed in the quality of depressive manifestations. Thus, if at the time of involvement in the study all participants recorded subclinical depressive manifestations, then after 60 days the absence of depressive symptoms was observed in 60 participants of the intervention group, and subclinical depressive manifestations - in 10 participants, while in the control group the spontaneous reduction of depressive manifestations during the time and, accordingly, their absence were observed in 17 participants, and subclinical depressive manifestations - in 53 (Fig. 2). This difference was also statistically significant ($\chi^2 = 50.90$; $p < 0.000$).

The median value of the indicator on the SSS-8 scale also differed between the groups by 8 points, statistically significant ($p < 0.000$) smaller results were also observed in the intervention group (Fig. 3), which reflected a decrease in the degree of somatic manifestations in this group.

Differences were also observed in the mean score on the QOLS. The average values of the two groups differed by 10.04 in favor of the intervention group (Fig. 4), this difference was also statistically significant ($p < 0.000$).

When comparing the indicators of the intervention group on the 1st (T1) and 60th day (T2) of participation in the study, the statistically significant changes ($p < 0.000$) were observed in all three indicators (Table V).

The depressive symptoms dynamics graph (Fig. 5) allows us to visually estimate that for 60 days of using the Deprilium® complex we observed a decrease in the severity of symptoms by ≈66% (decrease in the median value by 6 points).

The decline on the SSS-8 scale was even greater (decrease in the median value by 7 points) - by ≈73% (Fig. 6).

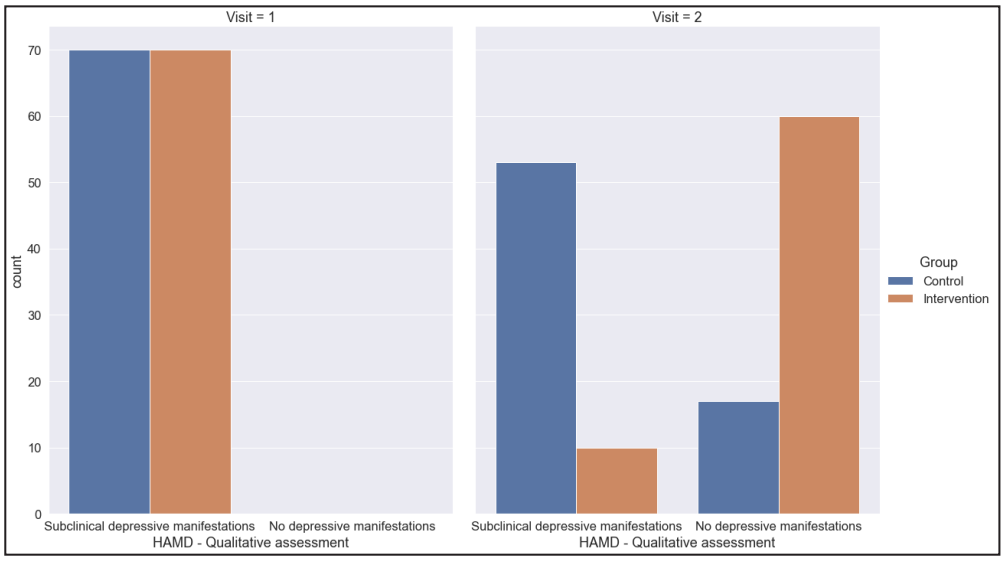

Fig. 2. Qualitative assessment of HAM-D clinical depression scale in the intervention group and the control group on the 1st and 60th day of the study

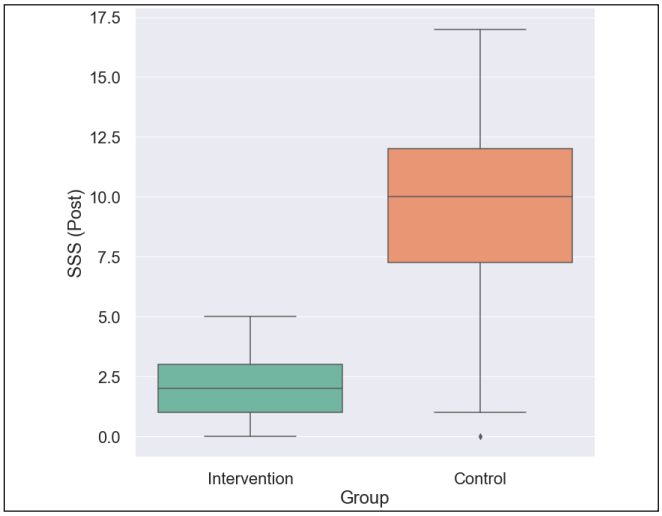

Fig. 3. Median values and interquartile range on the SSS-8 in the control group and the intervention group

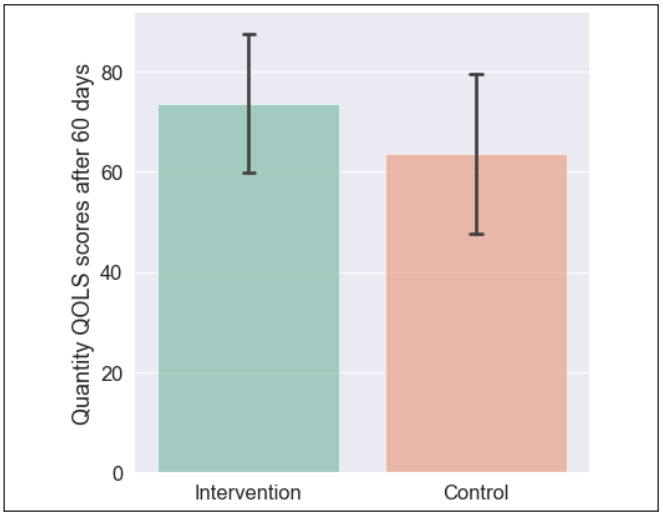

Fig. 4. Mean values and standard deviation of quantity QOLS scores after 60 days in the control group and intervention group

As a result, somatic manifestations in patients from the intervention group decreased significantly ($p < 0.000$). The minimum level of somatic manifestations was recorded in 67 (95%) patients, low - in 3 (5%). In the control group after 60 days there were minimal somatic manifestations in 7 (10%) patients, low – in 11 (15%), medium - in 29 (41%), high - in 18 (25%), very high - in 5 (5%) patients. Visual assessment of the data is presented in Fig. 7.

The increase in indicators was also observed on the QOLS (increase of the average value by 9.9 points) - by ≈13.5% (Fig. 8)

Thus, there was an improvement in the quality of life of patients. After 60 days, 9 (12.9%) participants had a very low level of quality of life, low - 15 (21.4%) participants, medium - 14 (20%), high - 11 (15%), very high - 21 (30%). For comparison, in the control group after 60 days in 19 (27.1%) people a very low level of quality of life was noted, low - in 20 (28.6%), medium - in 18 (25%), high - in 5 (7%), very high - in 8 (11%). This difference between groups was statistically significant ($p < 0.000$). Visual data evaluation is presented in Fig. 9.

Adverse events such as nausea, weakness, decreased blood pressure, diarrhea, itchy skin were more common in the intervention group over the 60 days. Feelings of increased heart rate and anxiety were observed more often in the intervention group. However, statistical processing did not reveal significant differences between the groups (for all cases $p > 0.05$). Results are presented in table VI.

DISCUSSION

The results suggest that the Deprilium® complex is much better than placebo at helping reduce subclinical depressive manifestations in patients with NCD. Although adverse effects were more common

Table III. Indicators of the two groups prior to randomization

Scale	Intervention group (n=70)	Control group (n=70)	t / W	p
HAM-D	9 [8-10]	9 [8.25-9]	W = 2154	0.347
SSS-8	8.52 ± 3.77	9.44 ± 3.69	t = -1.44	0.150
CQOLS	63.72 ± 14.70	61.35 ± 14.72	t = 0.95	0.345

Table IV. Comparison of the two groups on day 60

Scale	Intervention group (n=70)	Control group (n=70)	The difference in the median (Intervention group: control group)	T /W	p
HAM-D	3 [1-6]	9 [8-11]	-6	W = 378	0.000
SSS-8	2 [1-3]	10 [7.25-12]	-8	W = 263	0.000
CQOLS	73.62 ± 13.90	63.58 ± 16.07	+8	t = 3.95	0.000

Table V. Changes in mean values on the 1st and 60th day of the study

Scale	T1 (n=70)	T2 (n=70)	Difference in average/ median	t/W	p
HAM-D	9 [8-10]	3 [1-6]	-6	V = 2275	0.000
SSS-8	9.5 (6.25-9.5)	2 [1-3]	-7	V = 2200.5	0.000
CQOLS	63.72 ± 14.70	73.62 ± 13.90	+9.9	t = 5.56	0.000

Table VI. Frequency of adverse effects in the intervention group and the control group

Variable	Intervention group (n=70)	Control group (n=70)	χ^2	p
Nausea	4 (5%)	2 (2%)	0.174	0.676
Feeling of weakness	5 (7%)	3 (4%)	0.132	0.716
Bounding pulse	1 (1.4%)	2 (2%)	0	1
Decrease of the arterial blood pressure	2 (2%)	1 (1.4%)	0	1
Diarrhea	2 (2%)	0 (0%)	0.507	0.476
Itchy skin	3 (4%)	1 (1.4%)	0.257	0.612
Anxiety	1 (1.4%)	2 (2%)	0	1

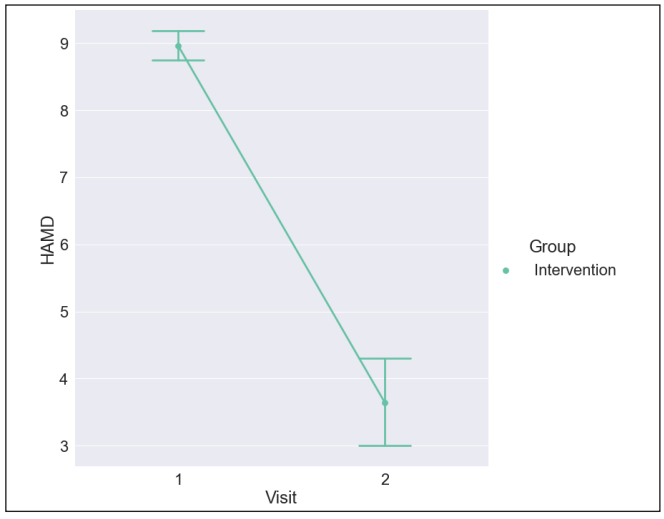

Fig. 5. Dynamics of indicators on the HAM-D scale in the intervention group for 60 days

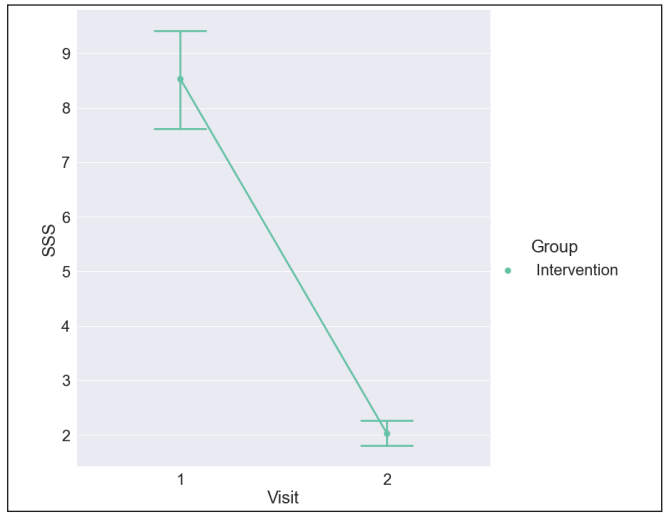

Fig. 6. Dynamics of indicators on the SSS-8 scale in the intervention group for 60 days

in the intervention group, the statistically significant difference with the control group was absent.

There are many approaches to treatment of patients with depression, so each new strategy must be evaluated from

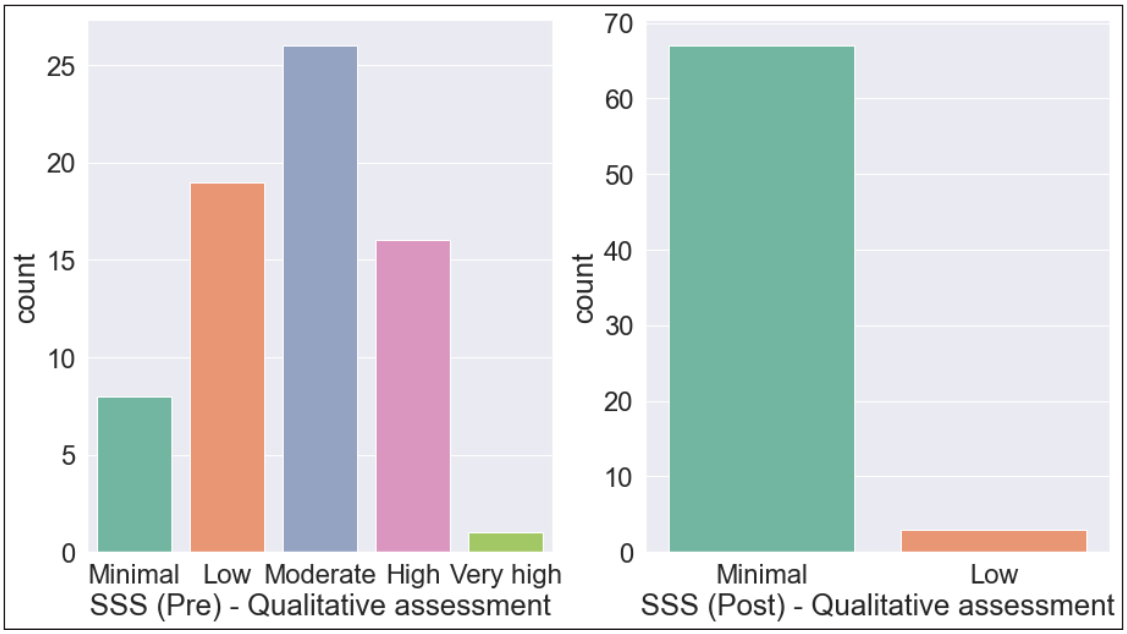

Fig. 7. Qualitative evaluation of somatic manifestations on the SSS-8 scale in the intervention group after 60 days

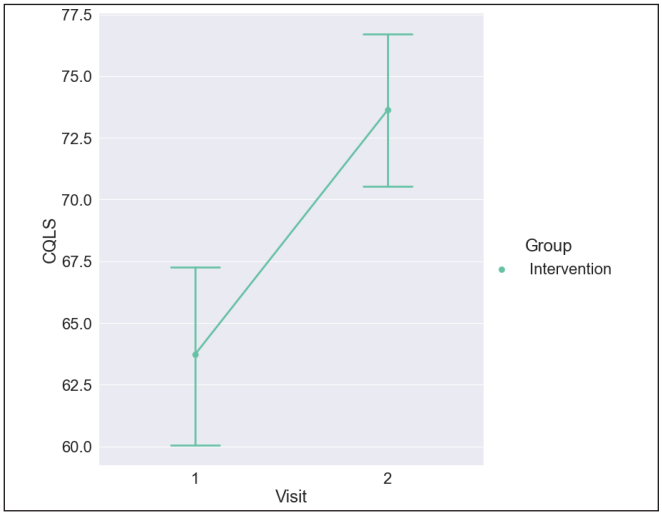

Fig. 8. Dynamics of the indicators on the QOLS scale in the intervention group for 60 days

the standpoint of weighing the risks and potential benefits [23]. Our results are consistent with the results of J. Sarris and co-authors (2014), who obtained similar SAMe efficacy results in major depressive disorder and used a similar design [19], and the results of K.M. Bell and co-authors (1994), who proved that the reduction in depressive symptoms by HAM-D scale is associated with increased concentration of SAMe in blood plasma [20]. Results regarding the side effects are also consistent with the reports of other researchers on the absence of clinically significant side effects reactions [22]. Given that the properties of SAMe can be compared with the effect of standard tricyclic antidepressants and selective serotonin reuptake inhibitors with a small number of side effects [9, 21], this makes it potentially important for the treatment of patients with early subclinical manifestations of depression in patients with NCD.

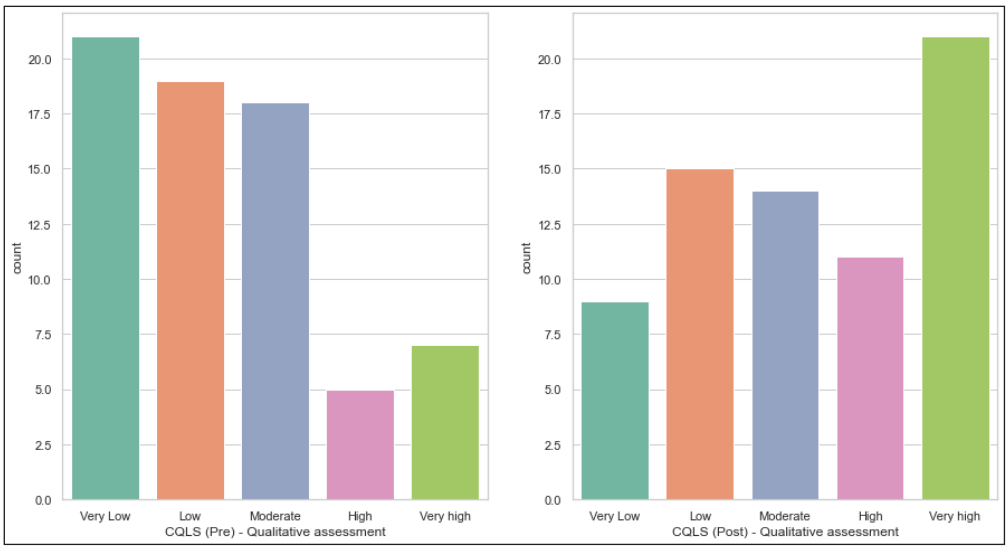

Fig. 9. Qualitative evaluation of quality of life on the QOLS in the intervention group after 60 days.

The advantages of this study are the design of a randomized controlled trial with double-blindness and a sufficiently long period of use of the Deprelium® complex to identify properties in comparison with placebo. Among the limitations of this study is the lack of follow-up evaluation, which makes it impossible to compare the effectiveness of therapy and durability of effects over time. Another limitation is a certain diversity in the group in terms of NCD, so further studies to provide deeper understanding of the properties and safety of the Deprelium® complex in some homogeneous clinical populations will supplement the obtained results. Also, the data of this study cannot be generalized to populations of adolescents and the elderly due to the age composition of the study participants (adulthood).

CONCLUSIONS

The results we have obtained confirm the available evidence on the effectiveness of SAMe in the treatment of patients with depression and provide the evidence of the properties of the Deprilium® complex containing SAMe and L-methylfolate with methylcobalamin, which together cause pharmacological and clinical synergy aiming to help reduce the severity of subclinical depression manifestations in patients with common NCD. In addition, it was found that the use of Deprilium® for 2 months does not carry increased risk to patient health and does not have significant side effects. Further studies are needed to research the use of the Deprilium® complex for patients with NCD.

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Conflict of interest:

The Authors declare no conflict of interest.