The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 897- 904

Efficacy of Non-Invasive Vagus Nerve Stimulation for Depression in Elderly

Ahmed Talaat El Sayed*[1], Akram Abd Al Aziz Sayed[2], Mohamed Mortada Mohamed Goda[3], Saif Mehmed[2,4]

[1]Department of Physical Therapy Nozha Medical Sector, Ministry of Health, Cairo, Egypt

[2]Department of Physical Therapy for Cardiovascular Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, Cairo University, Egypt

[3]Department Geriatrics and Gerontology, Faculty of Medicine, Ain Shams University, Egypt

[4]Department Cardiovascular Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, AlSalam University, Egypt

***Corresponding author:** Ahmed Talaat El Sayed, **Mobile:** (+20) 01004370080, **E-mail:** ahmedelsayed4066@gmail.com

ABSTRACT

Background: Depression is one of the common mental illnesses affecting over 300 million subjects all over the world and has been considered a main cause of disability in recent years.

Objective: To investigate the effect of non-invasive vagus nerve stimulation (NVNS) for depression in elderly.

Patients and Methods Forty patients diagnosed with depression; their age 60-70 years old. They were selected according to inclusion criteria from Matareya Teaching Hospital and were divided into two groups equal in number Group **A (Study group):** Twenty **(**20) patients received vagus nerve stimulation as adjuvant to standard medical treatment and psychotherapy. Group **B (Control group):** Twenty **(**20) patients received standard care for major depressive disorder (MDD) patients in the form of medical treatment and psychotherapy.

Results: There was statistically significant difference between two groups in the form of improvement the Hamilton Depression Rating Scale post treatment for group A and laboratory results of C-reactive protein (CRP), pro-inflammatory interleukin (IL)-6, IL-1, tumor necrosis factor-alpha (TNF-α), Serotonin post-treatment for group A in comparison to other group who did not receive non-invasive vagus nerve stimulation.

Conclusion: Use of NVNS for elderly patients with depression is an effective additional adjuvant intervention to alleviate symptoms and reduce the severity of the disease.

Keywords: Depression, NVNS, the HAMD, TNF-α, Interleukin.

INTRODUCTION

Persistent manifestations of poor mood, low self-esteem, and loss of interest or pleasure in pleasurable activities are hallmarks of Major depressive disorder (MDD), commonly referred to as clinical depression. In the 1980 edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), the American Psychiatric Association accepted the term, which was first utilized by a group of US clinicians in the mid-1970s, for this cluster of symptoms under mood disorders. Since then, it has been used extensively [(1)].

Anhedonia, low energy, rumination, decreased cognition, vegetative symptoms, and suicidal thoughts are some of the symptoms of MDD, a prevalent, expensive, and possibly fatal mental disorder. inclination [(2)].

According to the subject's claimed experiences, behaviour as defined by friends or family, and a mental health assessment, MDD is diagnosed. Even though the ailment cannot be tested in a lab, physical disorders that might produce comparable manifestations could be excluded. Females are afflicted almost twice as frequently as males, and the most common beginning time is in the 20s [(3)]. From a single, months-long episode to a chronic illness with repeated severe depressive episodes, the disorder's course differs significantly. Antidepressant drugs and psychotherapy are commonly used to treat MDD [(4)].

Although medication seems to be helpful, only the most profoundly depressed people may see a noticeable impact. In conditions when there is a substantial risk of injury to oneself or others, as well as accompanying self-neglect, hospitalization—which may be involuntary—may be required. If alternative treatments don't work, electroconvulsive therapy (ECT) could be taken into consideration. With around 40% of the risk being hereditary, MDD is believed to be brought on by a confluence of psychological, environmental, and genetic variables. A family history of the illness, considerable life changes, particular medications, long-term health issues, and substance use disorders are predisposing factors [(5)].

The WHO rated MDD as the third main cause of disease burden globally in 2008 and by 2030; it is expected to top the list. Anhedonia, or a diminished interest in pleasurable activities, feelings of guilt, a lack of energy, difficult concentration, appetite changes, psychomotor retardation or agitation, sleep abnormalities, or suicidal ideation, are all indicators that someone has this disorder. A subject must demonstrate five of the above-mentioned symptoms, such as a sad mood or anhedonia that interferes with social or professional functioning, to be diagnosed with MDD, based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). A history of manic episode must be excluded before the confirmation of MDD diagnosis [(6)].

Depression affects around 7% of those over 60, and older persons are more likely to have treatment non-response to first-line medication and/or psychotherapy [(7)]. Age-related physiologic alterations that make older cases more prone to antidepressant

Received: 23/09/2024
Accepted: 01/12/2024

adverse events and less likely to accept the right amount of medication may be the reason of this elevated level of treatment non-response. Furthermore, older persons are more likely to have polypharmacy, which raises their risk of cognitive and physical impairments [(8)].

Antidepressant drugs, psychotherapy, cognitive behavioural therapy, deep brain stimulation, electroconvulsive treatment, and repeated transcranial magnetic stimulation are the most often utilized therapeutic approaches for MDD [(9)].

Nevertheless, antidepressant drug response rates are inadequate, and up to 35% of cases continue to have recurrent and treatment-resistant MDD [(10)].

In terms of treatment-resistant depression (TRD), vagus nerve stimulation (VNS) is a comparatively new Food and Drug Administration (FDA)-approved somatic therapy that has the potential to provide substantial and clinically relevant antidepressant benefits [(11)]. VNS's proven anti-inflammatory properties may be a major factor in its effectiveness in treating individuals who did not react to antidepressants [(9)].

Stress-mediated depression is one of the main mental diseases with a high incidence and suicide rate; there is a lack of efficient therapy. As a result, efficient therapies with little unwanted effects are urgently required. PICs, or pro-inflammatory cytokines, could be important in stress-induced depression. Higher amounts of IL-1β, TNF-α, and IL-6 have now been discovered in the peripheral blood and brain tissue of depressed subjects in both preclinical and clinical investigations. According to recent research, PICs impact neuroinflammation, monoamine neurotransmitters, the hypothalamic pituitary-adrenal axis, and neuroplasticity, all of which contribute to depression. Additionally, they have a significant impact on the onset, course, and symptoms of depression and might serve as a marker for depression diagnosis and treatment. Furthermore, elevated PIC levels can be somewhat alleviated by well-established antidepressant treatments [(12)].

A bipolar electrode is surgically positioned on the left vagal nerve and linked to a stimulator in the chest wall as part of the FDA-approved VNS therapy. For persistent depression, VNS is usually utilized as a long-term supplementary therapy [(10)].

The major open-label trial demonstrated a 16% remission rate and a 27% responder rate. Patients with TRD who got adjunctive VNS had better five-year results than the treatment-as-usual group, which included cases who had formerly had ECT, according to a five-year observational trial that was carried out at 61 locations and involved 795 patients [(13)]. A new meta-analysis includes 22 papers (2 RCTs, 16 single arm and 4 non-randomized comparative studies) that support VNS as an effective therapy for persistent depression [(14)]. We aimed to investigate the effect of NVNS for depression in elderly.

PATIENTS AND METHODS

Participants:

Divided into two groups equal in number; Group A (Study group): Twenty (20) patients received vagus nerve stimulation as adjuvant to standard medical treatment and psychotherapy. Group B (Control group): Twenty (20) patients received standard of care for MDD patients in the form of medical treatment and psychotherapy.

Inclusion criteria:

- Aged between 60 and 70 years old.
- Meeting ICD-10 diagnostic (2 typical and 2-3 additional core symptoms).
- Symptoms of depression have been present for at least 2 months but less than 2 years.
- Agreed to use the non-invasive VNS device as instructed and met study conditions.
- All patients received their medications according to doctor's instructions.

Exclusion criteria:

- Unable to cooperate with the study protocols.
- Currently participating in a non-invasive VNS clinical experiment.
- A history of brain tumors, aneurysms, intracranial hemorrhages, or severe head trauma.
- Recent myocardial infarction, congestive heart failure, severe coronary artery disease, severe atherosclerosis, or carotid artery disease.
- High blood pressure that is not under control.
- Belonged to a vulnerable group or had a health issue that interfered with their capacity to give informed consent, adhere to follow-up protocols, or offer self-evaluation.

Participants assessment:

The following was done before starting non-invasive (VNS**)** and after four weeks of non-invasive (VNS**)** sessions using transcutaneous electrical nerve stimulation device.

The Hamilton Depression Rating Scale (HAMD):

Laboratory assessment:

- CRP levels.
- PICs (TNF-α, IL-6, and IL-1).
- Serotonin.

Treatment instruments:

- NVNS using transcutaneous electrical nerve stimulation (TENS) device.

Treatment procedure:

Group A: participants were given NVNS by TENS device for 30 minutes over the carotid sheath in the cervical region bilaterally one session per day for a successive 5 days weekly for four weeks.

Group B (Control group): received standard of care for **(MDD)** patients according to routine clinical standards for **(MDD)** as described by hospital protocol one session per day.

Outcome measures: the HAMD were measured for the two groups as baseline then follow up assessment of the HAMD after four weeks of NVNS and other added measures were laboratory measures of CRP, PICs, such as TNF-α, IL-6, IL-1, serotonin as baseline then follow up assessment after four weeks of NVNS**.**

Ethical approval:

The Research Ethics Committee of Cairo University's Faculty of Physical Therapy has authorized the current study [No: P.T.REC/012/003901]. Each participant completed a permission form when all information was received. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

The SPSS software, version 20, was utilized to analyze the data. Qualitative data were presented as frequency and percentage and were compared using X^2-test. Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to determine if the quantitative data distribution was normal. To examine the impact of the measured variables (Hamilton depression score, CRP, TNF-α, IL-6, IL-1, serotonin) both within and between groups MANOVA was used. Quantitative data were presented as mean ±SD, and were compared using the paired t-test to evaluate the statistical significance of the difference between the pre and post treatment in each group, and the independent student t-test to examine the mean difference between the two groups. A value of $P<0.05$ was deemed significant.

RESULTS

Demographic data of subjects:

A total of 40 patients contributed to this study; they were allocated into 2 equal groups; group (A) **(study)** consisted of 20 patients received NVNS, and group (B) **(control group)** consisted of 20 cases received standard of care for **MDD** cases. As demonstrated in table (1) and figures 1-2; there wasn't significant difference between the mean value of age of both groups as well as sex distribution, between both groups.

Table (1): Demographic data of participants of both groups.

Demographic data	Group A (N=20)	Group B (N=20)	t-value	p-value
Age (years)	64.4±2.9	64.5±3.2	-0.05	0.959
Sex Males Females	N (%) 13 (65%) 7 (35%)	N (%) 12 (60%) 8 (40%)	χ^2= 0.107	0.744

*Significant.

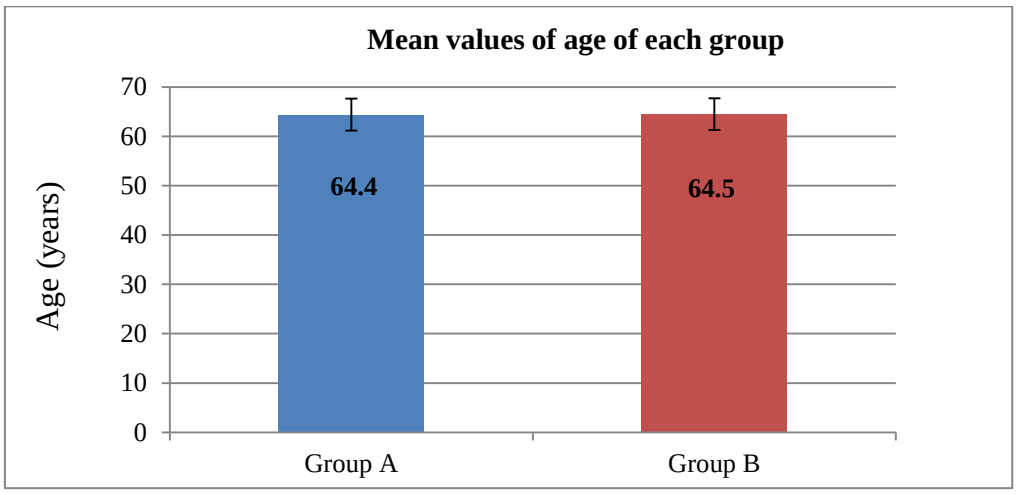

Figure (1): Mean values of subjects age of each group

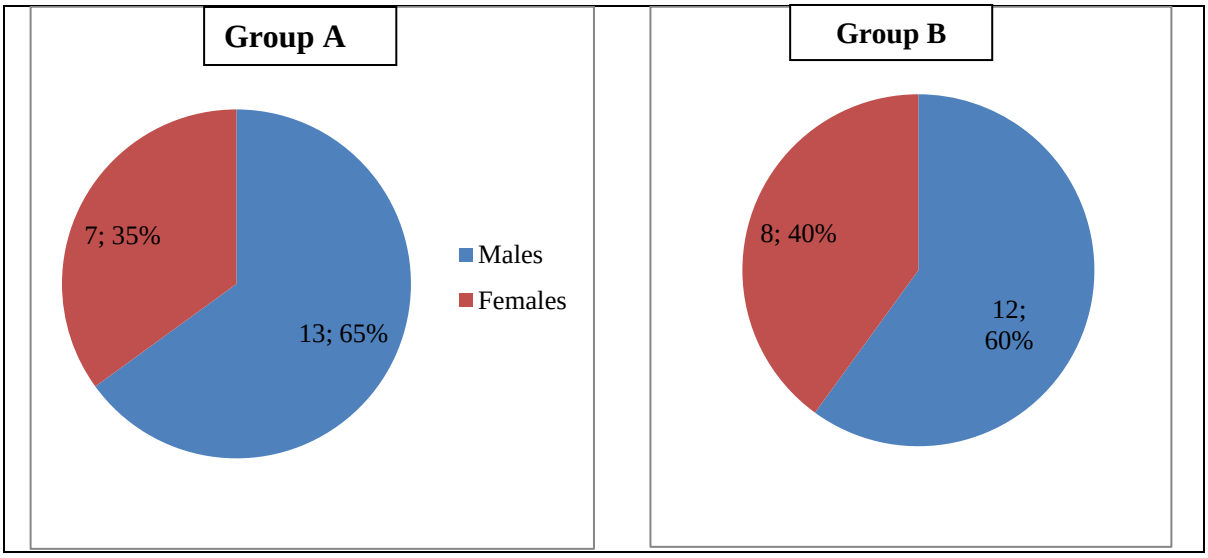

Figure (2): Sex distribution of each group

There wasn't a significant difference in the mean values of Hamilton depression score pre-treatment between both groups, whereas there was a significant difference post-treatment between both groups in favor to group A (Table 2, figure 3 and 4).

Table (2): Comparison between our study participants pre and post treatment as regard HAMD.

Measured variables	Group A Mean ±SD	Group B Mean ±SD	Mean difference	F-value	P-value	η^2
Hamilton depression score Pre-treatment	22.15 ± 3.69	23.05 ± 3.76	-0.9	0.58	0.450	0.15
Post-treatment	9.95 ± 2.74	15.55 ± 2.67	-5.6	42.88	0.001*	0.53
% of change	55%	32%				
P-value[1]	0.001*	0.001*				

*Significant.

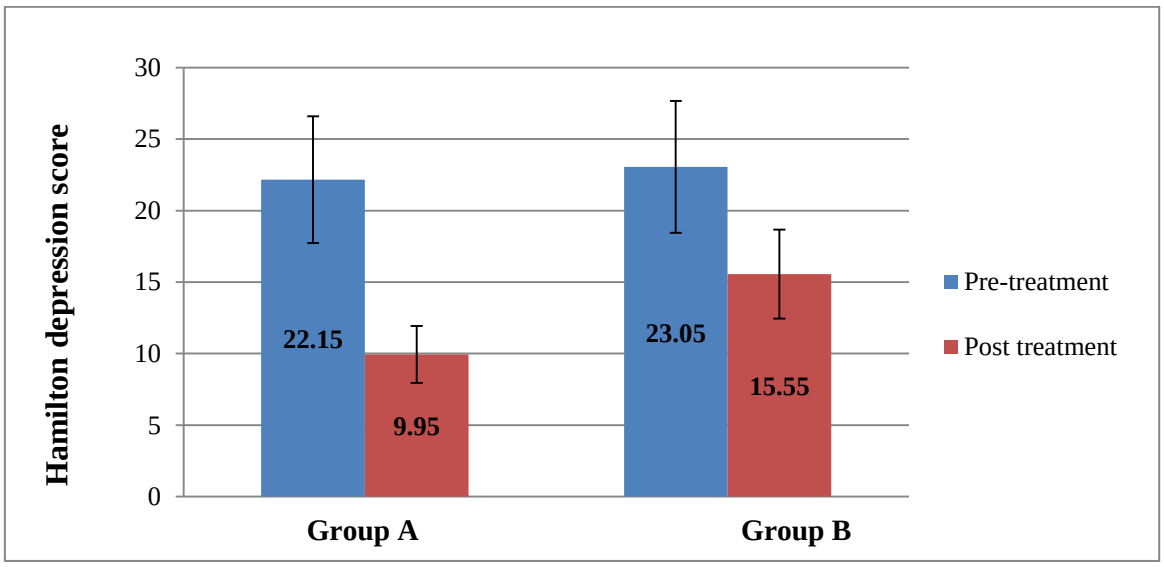

Figure (3): Comparison of mean values of Hamilton depression score pre and post treatment within each group

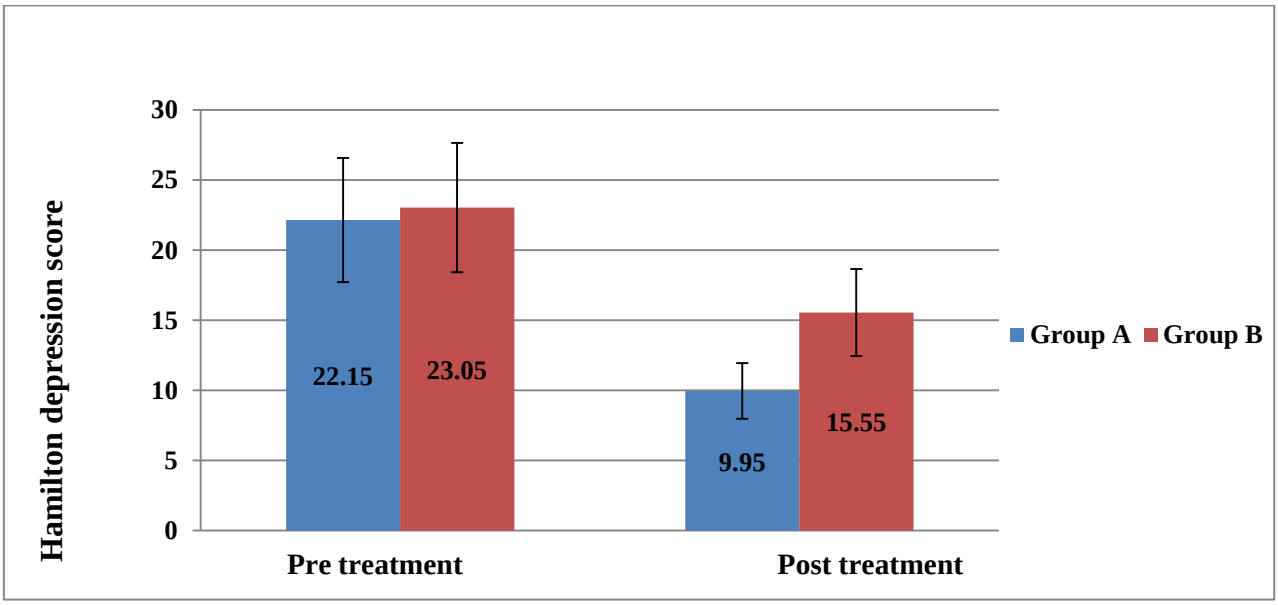

Figure (4): Comparison of mean values of Hamilton depression score pre and post treatment between groups.

Table (3): Comparison between our study participants pre and post treatment as regard laboratory analysis.

Measured variables	Group A Mean ±SD	Group B Mean ±SD	Mean difference	F-value	P-value	η^2
CRP (mg/L)						
Pre-treatment	14.35 ± 2.92	13.45± 2.76	0.9	1	0.323	0.03
Post-treatment	8.5 ± 1.32	9.9 ± 1.41	-1.4	10.5	0.002*	0.22
% of change	41%	26%				
P-value[1]	0.001*	0.001*				
TNF (pg/mL)						
Pre-treatment	18.05 ± 4.21	19.1 ± 1.97	-1.05	1	0.319	0.03
Post-treatment	12.2 ± 3.44	16.55 ± 2.82	-4.35	19.2	0.001*	0.34
% of change	32%	13%				
P-value[1]	0.001*	0.001*				
IL-1 (pg/mL)						
Pre-treatment	7.3 ± 1.78	8.25 ± 1.68	-0.95	3	0.091	0.07
Post-treatment	4.1 ± 1.25	5.4 ± 1.1	-1.3	12.2	0.001*	0.24
% of change	44%	35%				
P-value[1]	0.001*	0.001*				
IL-6 (pg/mL)						
Pre-treatment	19.6 ± 3.2	19.95 ± 4.42	-0.35	0.08	0.776	0.002
Post-treatment	12.25 ± 2.53	15.05 ± 3.69	-2.8	7.8	0.008*	0.17
% of change	38%	25%				
P-value[1]	0.001*	0.001*				
Serotonin (ng/mL)						
Pre-treatment	47.1 ± 11.79	50.35 ± 11.25	-3.25	0.79	0.378	0.02
Post-treatment	64.5 ± 11.49	55.75 ± 11.13	8.75	5.98	0.019*	0.14
% of change	37%	11%				
P-value[1]	0.001*	0.001*				

SD: standard deviation, *: significant, p value: Probability value, η2: partial eta square

DISCUSSION

In 2001 MDD ranked as the fourth most common cause of disability globally [15], it is expected to rise to the second position by 2020 [16]. With regard to psychological, physical, and social functioning, patients with MDD have a worse quality of life, and this impairment gets worse as the disease gets worse [17].

Despite being treatment of choice therapy for depression, up to 68% of cases discontinue antidepressant medication after three months [18]. One-third of individuals with MDD will attain remission with any particular antidepressant, and around 50% of cases will respond to first-line antidepressant medication; however, 50% of these cases will relapse throughout current treatment before they recover [19]. Therefore, present MDD therapies are far from acceptable, despite the urgent need [16].

Clinically meaningful antidepressant benefits can be obtained via VNS, an FDA-approved somatic therapy for TRD [11]. However, this therapy is only available to MDD cases who are managed for depression but haven't responded to at least four prescription drugs and/or proven somatic treatment methods like ECT [20]. This is due to the surgical risks and possibly serious adverse effects.

The "bottom-up" process of the central nervous system suggests that electric impulses may go in the opposite direction from peripheral nerves to the brain stem and core structures [21]. Accordingly, direct stimulation of the ear's afferent nerve fibers ought to have a depressed symptom-reduction effect comparable to that of traditional VNS without the need for surgery [22].

Although VNS has been used clinically for MDD patients, its underlying mechanism is still unclear [19]. Theories are predicated on how the vagus nerve's structure and functional alterations affect mood regulation [23]. About 80% of the mixed nerves that makes up the vagus nerve are afferent fibers. The projection of afferent fibers to the nucleus tractus solitaries (NTS), which is subsequently linked directly and indirectly to cerebral regions like the amygdala, hypothalamus, insular lobe, thalamus, orbitofrontal cortex (OFC), and different limbic areas in charge of mood and anxiety regulation, is thought to be partially responsible for the antidepressant effects of VNS [24].

Additionally, electrophysiological research has demonstrated that VNS raises the firing rate of serotonergic neurons after 14 days and noradrenergic neurons after 1 day of treatment [25]. In rats, VNS also raises the extracellular norepinephrine levels in the cortical and hippocampal regions [26]. Furthermore, it has been discovered that serotonergic neurons are activated by the VNS stimulatory settings employed in depressed patients [25].

The solitary tract nucleus, which has secondary projections to limbic and cortical areas comprised in mood regulation, is thought to be stimulated by VNS in order to produce its positive effects. Numerous neurochemical alterations, such as those pertaining to neurotransmission and growth factor synthesis, are brought about by the activation of these brain regions [27]. Similar to other depression treatment methods, functional imaging studies indicate that while chronic VNS significantly deactivates ventromedial prefrontal cortex, it causes acute alterations in the hypothalamus, OFC, amygdala, hippocampus, insular lobe, medial prefrontal cortex, and cingulated [28]. Nonetheless, it is hypothesized that the vagal efferent pathway's activation and the ensuing suppression of peripheral inflammation account for at least some of the positive effects of VNS in depressed individuals [29].

The current study was randomized controlled trial and blinded study. Forty volunteers diagnosed with depression their aged 60-70 years old. They were selected according to inclusion criteria from Matareya Teaching Hospital and were divided into two groups equal in number: **Group A (Study group):** Twenty **(**20) patients received VNS as adjuvant to standard medical treatment and psychotherapy. **Group B (Control group):** Twenty **(**20) patients received standard of care for **(MDD)** patients.

Our study showed that there was a significant positive effect of NVNS using TENS device as adjuvant to standard medical treatment and psychotherapy in treatment of MDD.

Our study results matching the study by **Müller *et al.*'s study** [30], 20 TRD patients received treatment using both low-strength/high-frequency (HF) VNS (≤1,5 mA, 20 Hz) and high-strength/low-frequency (LF) (>1,5 mA, 15 Hz). Patients who received treatment using the low-strength/HF stimulation settings showed a significant reduction in their HAMD. Patients receiving high-strength/LF combo treatment showed no improvement in their ratings. During the follow-up period, 60% of cases received low-strength/HF stimulation at 30 Hz and 0.65±0.35 mA. When the patient showed signs of HAMD worsening, the frequency was the first parameter to be raised. The only things preventing from employing 30 Hz stimulation in certain individuals were side effects, such as changes in voice.

A noteworthy improvement in HAMD to a mean of 10.2 points was noted in Sperling open-label case control research with a follow-up length of up to one year, in which the cohort comprised 18 patients with TRD and the identical VNS settings [31].

At the conclusion of the twelve-week acute phase, the pilot study's response rates— described as a 50% or higher decrease in the 28-item HRSD and remission—were 30.5% and 15.3%, respectively. Remission was described as a score of less than ten on the HRSD. The response rate rose to 44% after a year of supplementary VNS therapy, and it was mostly maintained after two years of active treatment. Remission rates significantly improved, rising from

15.3% following acute phase therapy to 27% after 9 months and 22% at 2 years [32].

Although there is no particular evidence on senile patients with depression, VNS has been licensed in the USA as an adjuvant therapy for TRD. The lack of agreement regarding the ideal stimulation settings may be the reason why results from research examining the effectiveness of VNS in mixed age groups are still unclear. Although there was a notable improvement independent of electrical dosage intensity, the first randomized research to thoroughly examine responsiveness to different doses of VNS indicated that the duration of response was much larger with high and medium doses [33].

An RCT of ten weeks of therapy with VNS vs sham stimulation was conducted in light of the findings of previous open studies evaluating the short-term (ten weeks) effectiveness of VNS in patients with TRD, which demonstrated an average response rate of 35% [19]. VNS generated a response rate of 15.2% on the principal HAMD response measure, compared to 10% in the sham group; this difference wasn't statistically significant. Nonetheless, there were notable variations in response rates using a supplementary outcome measure. This is the only RCT to date that compares VNS versus sham stimulation. This unfavorable outcome and the significant variation in efficacy among the trials have received the attention they deserve [34].

Aaronson *et al.* [33] conducted a 50-week study, in a five-year follow-up to their earlier trial evaluating the effects of VNS or TAU in individuals with TRD. The longest treatment period to date is seen in this research. In line with their previous findings, the group that received adjunctive VNS outperformed the group that received TAU in terms of outcomes. The VNS group had a significantly greater five-year cumulative response rate (67.6% versus 40.9%) and a significantly greater remission rate (cumulative 1st-time remitters, 43.3% versus 25.7%) than the TAU group.

CONCLUSION

Use of NVNS for elderly cases with depression is an effective additional adjuvant intervention to alleviate symptoms and reduce the severity of the disease.

No funding.
No conflict of interest.

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