Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: a nonrandomized controlled pilot study

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Abstract

Background—Depression presents a significant burden to both patients and society. One treatment that has emerged is vagus nerve stimulation (VNS), an FDA-approved physical treatment for depressive disorders. However, the application of this intervention has been limited by the involvement of surgery and potential side effects. The aim of this study is to explore the effectiveness of stimulating the superficial branches of the vagus nerve as a solo treatment for MDD.

Methods—This is a nonrandomized, controlled study. The first cohort of patients (n = 91) only received transcutaneous auricular VNS (taVNS) for 12 weeks. In the second cohort (n = 69), patients first received 4 weeks of sham taVNS followed by 8 weeks of taVNS. All treatments were

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self-administered by the patients at home after they received training from the hospitals. The primary outcome measurement was the 24-item Hamilton Depression Rating Scale measured at weeks 0, 4, 8, and 12. Data analysis included a timelag analysis comparing 1) real and sham taVNS groups at week 4; 2) the real taVNS group at week 4 vs the sham taVNS group at week 8 (fourth week of real taVNS following 4 weeks of sham); and 3) the real taVNS group at week 8 vs the sham taVNS group at week 12 (eighth week of real taVNS following sham).

Results—After four weeks of treatment, MDD patients in the taVNS group showed greater improvement than that of the sham taVNS group as indicated by both Hamilton score changes as well as response and remission rates at week four. In addition, we also found that the clinical improvements continued until week 12 during taVNS.

Limitations—Patients were not randomized in this study.

Conclusions—Our results suggest that taVNS is a promising, safe, and cost-effective therapeutic method for mild and moderate MDD.

Keywords

Introduction

Major depressive disorder (MDD) is the fourth leading cause of disability worldwide (Sackeim and Lisanby, 2001) and is projected to become the second leading cause of disability worldwide by the year 2020 (Michaud et al., 2001; Rush, 2003). Patients with MDD experience reduced quality of life in terms of psychological, physical, and social functioning, and this impairment increases with the severity of the disease (Daly et al., 2010). Antidepressant medication is considered as afirst-line treatment for depression, yet up to 68% of patients stop taking antidepressants within 3 months (Gartlehner et al., 2011). Approximately 50% of patients with MDD will experience a response to first-line antidepressant therapy and one-third of patients will achieve remission with any given antidepressant, but half of these patients will experience a relapse during continuous treatment before they achieve recovery (Rush et al., 2006). Thus, despite the critical need, current treatments for MDD are far from satisfactory (Rush, 2003; Sackeim and Lisanby, 2001).

Vagus nerve stimulation (VNS) is an FDA-approved somatic treatment for treatment-resistant depression (TRD) that can produce clinically significant antidepressant effects (Daban et al., 2008; George et al., 2003; Nemeroff et al., 2006; Sackeim and Lisanby, 2001). However, the surgical risks and potentially significant side effects have limited this treatment to MDD patients who have been treated for depression but failed to respond to at least 4 prescribed medications and/or established somatic treatment options such as electroconvulsive therapy (Fitzgerald, 2013; Ventureyra, 2000).

To overcome the potential barriers of applying VNS, a non-invasive transcutaneous vagus nerve stimulation (taVNS) method has been developed. Anatomical studies suggest that the

ear is the only place on the surface of the human body where there is afferent vagus nerve distribution (Henry, 2002; Peuker and Filler, 2002). According to the "bottom-up" mechanism of the CNS, the propagation of electric stimuli might follow an inverse path from peripheral nerves toward the brain stem and central structures (Shiozawa et al., 2014). Consequently, direct stimulation of the afferent nerve fibers on the ear should produce an effect similar to classic VNS in reducing depressive symptoms, but without the burden of surgical intervention (Hein et al., 2013; Rong et al., 2012). In past years, taVNS has been applied to treat disorders such as epilepsy (Rong et al., 2014a; Stefan et al., 2012) and pre-diabetes (Huang et al., 2014) and has also been applied to boost associative memory in older individuals (Jacobs et al., 2015).

In a previous study (Hein et al., 2013), investigators explored the therapeutic effect of taVNS on 37 patients suffering from MDD using an add-on design (antidepressant therapy + real or sham taVNS). After two weeks of treatment, the taVNS group showed significant improvement on the Beck Depression Inventory (BDI) as compared with the sham condition. However, there was no significant difference on the Hamilton Depression Rating Scale (HAMD). Although the pilot study demonstrated that taVNS had potential as an MDD treatment, the small sample size, short length of treatment, and potential confounding of different antidepressant therapies have limited the significance of the study.

In this study, we applied a nonrandomized, controlled clinical trial to investigate the antidepressant effect of solo taVNS treatment in mild or moderate MDD patients. In the first cohort, patients received taVNS for 12 weeks to test the effectiveness of the treatment. In the second cohort, patients began with four weeks of sham taVNS followed by 8 weeks of taVNS. We hypothesize that taVNS will produce greater improvement in depression patients as compared with sham taVNS.

Methods

This study was registered at the Chinese Clinical Trial Registry Center (ChiCTR-TRC-11001201). The Institutional Ethics Committee of the China Academy of Chinese Medical Sciences approved this study. All clinical investigative procedures were conducted according to the principles expressed in the Declaration of Helsinki. All patients signed a consent form prior to initiation of study procedures.

Due to ethical and safety concerns, we recruited two cohorts of patients. The patients in the first cohort received only real taVNS to test the effectiveness of the treatment; the patients in the second cohort received sham taVNS only for one month before shifting to real taVNS treatment for two months (Figure 1). The clinical outcomes (primary and secondary outcomes), inclusion and exclusion criteria, and the real and sham treatment procedures remain the same as originally registered. Some patients (n = 49) were also invited to participate in an fMRI study at baseline and after 4 weeks of treatment to investigate the brain resting state functional connectivity changes before and after one month of taVNS as compared to sham taVNS. Please see the original publication for more details (Fang et al., 2015). The present study will focus on the clinical outcomes of a 12-week treatment of the multiple-center clinical trial, which was not reported in the previous brain imaging study.

Inclusion criteria

1) Meets ICD-10 diagnosis standard of a depressive episode: mild (2 typical + 2 other core symptoms), moderate (2 typical + 3 other core symptoms); 2) HAM-D-24 score between 8 and 35; 3) 18–70 years of age; 4) Ceased taking anti-depressive or other psychiatric medications 2 weeks before beginning the intervention; 5) Junior high or higher level education (in order to understand the scales); 6) Exhibited symptoms for 2 weeks to 2 years.

Exclusion criteria

1) Ongoing addiction to drugs and alcohol; 2) Severe depression (HAM-D-24 score>35) or suicidal intent; 3) Bipolar disorder; 4) Organic mental disorder; 5) Drug-induced depression; 6) Seasonal affective disorder; 7) Severe medical disorders; 8) Pregnant women; 9) Postpartum depression; 10) Dementia or other cognitive disorders; 11) Patients who did not agree to sign the consent form.

Recruitment procedures

Investigators recruited patients with mild or moderate depressive symptoms from three participating hospitals through advertising and flyers. After passing a pre-screening performed by a qualified physician and in accordance with the inclusion and exclusion criteria, potentially eligible patients provided informed consent in the presence of a study physician.

Intervention and comparison

After receiving their group assignment, all patients were trained to apply taVNS or sham taVNS by themselves. Specifically, patients were trained on how to turn on/off the machine, how to apply the electrode to the ear and locate the stimulation position, how to increase the intensity, and how to fill out the diary booklet. The procedure was repeated until the subjects were capable of using the machine independently. The training process usually lasted about 40 minutes.

All subsequent treatments were self-administered by the patients at home, and assistance was available by phone or via site visits if patients had questions about treatment. Patients were also instructed to complete a patient diary booklet each day to describe any side effects corresponding with or temporally related to treatment. The investigators checked all booklets at assessments every four weeks to ensure compliance. All procedures performed in the sham taVNS treatment group were identical to the procedures for the taVNS group.

taVNS treatment

Location—The taVNS points are located in the auricular concha area, where there is rich vagus nerve branch distribution (Figure 2).

Intervention procedure—All treatments were applied with an ear vagus nerve stimulator developed through the cooperation of the Institute of Acupuncture and Moxibustion, China Academy to Chinese Medicine Science (Beijing, China) and Suzhou Medical Appliance Factory (Jiangsu Province, China) with special ear clips (electrodes) (Huang et al., 2014;

Rong et al., 2014b; Rong et al., 2012). Patients took a seated position or lay on their sides. After stimulation points were disinfected according to standard practice, ear clips were attached to the auricular concha. Similar to previous studies (Rong et al., 2014b; Rong et al., 2012), stimulation parameters included: 1) a 20 Hz continuous sinusoidal wave (wave width of 0.2 ms) (Aihua et al., 2014; He et al., 2013; La Marca et al., 2010; Wang et al., 2012), and 2) stimulation intensity increased gradually (starting from 0) to the highest point that the patients could tolerate (typically between 4–6 mA). Each treatment lasted for 30 minutes and was carried out twice a day (once in the morning, once after dinner) (Huang et al., 2014).

Sham taVNS treatment

Location—The stimulation points for sham taVNS are located at the superior scapha (outer ear margin midpoint), where there is no vagus nerve distribution (Figure 2). A specially designed ear clip (electrode) that looks identical to a real taVNS clip was applied for sham treatment.

Intervention procedure—All procedures and stimulation parameters in the sham taVNS treatment group were identical to those of the real taVNS group. After 4 weeks, patients shifted to taVNS treatment for 8 weeks by changing a pair of ear clips (electrodes) with a line designed specifically for real taVNS. To blind the patients, all patients were told that the line and clips would be regularly changed to ensure the reliability of stimulation.

Clinical outcomes

All endpoints were measured at weeks 0, 4, 8, and 12. The primary endpoint was the 24-item Hamilton Depression Rating Scale (HAM-D-24) (Tang, 1984) and the secondary endpoints included the Self-rating Depression Scale (SDS), 17-item Hamilton Anxiety Rating Scale (HAM-A-17), and Self-rating Anxiety Scale (SAS). At the end of weeks 4, 8, and 12, we also assessed the differences in treatment response and remission rates between the two groups using HAM-D-24, where a response is defined as a 50% or greater reduction in HAM-D-24 scores and remission is defined as HAM-D-24 scores of 7 or less. Trained interviewers blind to treatment condition conducted the evaluations.

Statistical analysis

The effect of taVNS was estimated by comparing HAM-D-24 score differences between Week 4 and Week 0 using mixed-model regression with hospitals, group (real and sham taVNS), and week (Week 0 and Week 4) as fixed effects and patients as a random effect on patients who completed the trial at week 4. The analysis was performed using R Version 3.1.0, with the lme4 (http://CRAN.R-project.org/package=lme4) and lmerTest packages (http://CRAN.R-project.org/package=lmerTest). For this model, the treatment effect is the group and time interaction; the between hospital treatment difference is measured by the group, time, and hospital interaction. We omitted data from hospital H3 for this analysis because all H3 patients received the real treatment. Similar analyses were also performed on other clinical outcomes.

In addition, we compared the categorical classification of treatment response between the real and sham taVNS groups including the data from all three hospitals. We define the treatment response as a 50% or greater reduction in HAM-D-24 scores following treatment. Response rates between the two groups were compared using the chi square (x^2) test.

Power calculation

Since no prior study had used taVNS as the solo treatment for MDD, as a novel treatment, we present here our power analysis for the primary outcome (HAM-D-24) at week 4. For comparison of the pre- and post-treatment differences between real and sham taVNS, with 91 patients in the taVNS group and 69 patients in the sham taVNS group, we will have 80% power to test the effect size of 0.45 between the two groups based on the two sample t-test at a significance level of 0.05.

Results

One hundred sixty participants enrolled in the study (n = 91 cohort 1, n = 69 cohort 2). 148 subjects completed the trial at week 4, and 138 completed the trial at week 12 (n = 84 cohort 1; n = 54 cohort 2). Seven participants from the taVNS group dropped from the study: five due to scheduling conflicts, one due to complete symptom relief before week 12, and one due to tinnitus enhancement resulting from incorrect manipulation of the equipment (symptoms were relieved after stopping treatment) (Figure 1). The whole study was performed between March of 2011 and December of 2013. Fifteen participants from the sham taVNS group withdrew from the study, all due to lack of a satisfactory effect. All other participants reported following the treatment instructions.

The baseline characteristics and clinical outcomes are shown in Table 1. The results showed no significant difference in age, gender, family history, HAM-D-24, SDS, and SAS between the real and sham groups at baseline. However, there was a significant difference on the HAM-A-17 level (p = 0.005).

Comparison between the taVNS and sham taVNS at week 4

We found that at week 4, the HAM-D-24 scores in both groups showed a decrease, but the reduction in the real taVNS group was significantly greater than in the sham taVNS group. In addition, we also found there was no significant interaction between group, time, and hospital interaction (p = 0.06). This trend toward significance can be explained by a difference in patients' depression severity at baseline between the two hospitals as indicated by HAM-D-24 scores (the following analysis showed that effect size tends to be larger in patients with higher HAM-D-24 scores). Thus, we re-ran the analysis, leaving the hospital out of the model. The significant treatment effect remained (Table 3).

To explore the treatment effect on the severity of patients' depression at baseline, we divided the patients into two subgroups based on HAM-D-24 score (mild subgroup, HAM-D-24 score < 20; moderate subgroup, HAM-D-24 score 20 group) (Tang, 1984). We observed a significant treatment effect in both the mild subgroup (p = 0.04, effect size 0.4) and the moderate subgroup (p < 0.0001, effect size 0.68).

The comparison of response rates (defined by 50% reduction in the HAM-D-24 score) showed that at week 4, there were 24 responders in the taVNS group and no responders in the sham taVNS group (Table 4). There was a significant difference between the two groups at week 4 (p < 0.00001). Interestingly, there was no significant difference in the response rate between weeks 0–4 in the taVNS group and weeks 4–8 in the sham taVNS group, after the patients had shifted to taVNS (p = 0.07). Similarly, there was no significant difference between the response rates of the taVNS group in weeks 4–8 and the sham taVNS group in weeks 8–12 (Table 4).

Remission (defined as a HAM-D-24 scores < 8) showed that 3 patients of the taVNS group achieved remission at week 4, while none did in the sham group (Table 4). There was no significant difference between the two groups (p = 0.148) at week 4. However, we found significant differences between weeks 0–4 and 8–12 in the taVNS group (p<= 0.0001), indicating a continuous increase in remission rate across different time points. There was no significant difference in the remission rate between weeks 0–4 in the taVNS group and weeks 4–8 in the sham taVNS group, after the patients had shifted to taVNS (p = 0.553). Similar results were also observed between weeks 4–8 in the taVNS group and weeks 8–12 in the sham taVNS group (p = 0.216) (Table 4).

Similar results were observed in secondary outcomes including SDS, SAS, and HAM-A-17, i.e., combining the two hospitals showed significant improvement at week 4 when comparing taVNS and sham taVNS (Table 3).

taVNS treatment effect at week 12

In this study, patients in the taVNS group received treatment for three months. The clinical outcomes for each month are shown in Figure 2. Data showed that symptom improvement as indicated by clinical outcomes as well as response and remission (Table 4) continued until the end of this study (week 12). Similar results were also observed in the sham group after it shifted to taVNS (Figure 3).

Safety

Based on the patients' booklets and verbal reports, the main side effect was tinnitus, as shown in the acceleration of original tinnitus (2 in the taVNS group, 3 in the sham taVNS group). All participants recovered fully from the adverse events after stopping the treatment.

Discussion

In this study, we investigated the treatment effect of solo taVNS on patients with mild or moderate MDD. We found that taVNS could significantly reduce the symptoms of depression in the three months during which the treatments were applied. More importantly, we found that the symptom reductions were greater in the taVNS group than in the sham taVNS group for the first four weeks when sham taVNS was applied.

In a previous pilot study (Hein et al., 2013), Hein and colleagues investigated the short-term (2 weeks) therapeutic effect of taVNS on patients suffering from major depression using an add-on design. They found that taVNS could significantly reduce BDI as compared with the

sham condition. However, there was no significant difference on the HAMD. In this study, we found that taVNS could not only reduce HAM-D-24 and SDS, but also reduce anxiety symptoms in these patients as indicated by HAM-A-17 and SAS in comparison with sham taVNS at week 4. These results may indicate that this method may also be extended to anxiety disorders in the future.

Moreover, we further analyzed the taVNS effect in subgroups of patients with different severity. Our results showed that although the effect size is smaller, taVNS can significantly reduce the HAM-D-24 score in those with relatively mild symptoms (HAM-D-24 < 20). Despite its considerable functional impairment (Cuijpers et al., 2004; Cuijpers et al., 2013; Hwang et al., 2015), mild MDD has usually not been viewed as responsive to antidepressants. Our results suggest taVNS may be considered as a first-line treatment targeting mild and moderate MDD.

In this study, we found significant differences in the response rate at week 4 between the two groups, which is consistent with findings of HAM-D-24 score changes. Nevertheless, we did not find significant differences in the remission rate at week 4 between the two groups, and we speculate this may due to a short observation time. Future studies with longer durations of sham treatment are needed. However, we did find significant improvement of the remission rate in the taVNS group across different time points, indicating that symptom relief continued across 12 weeks of treatment.

Despite the clinical application of VNS for MDD patients, its underlying mechanism is not yet fully understood (Rush, 2003; Rush et al., 2005a; Rush et al., 2005b). Hypotheses are based on the impact of anatomy and functional changes of the vagus nerve in mood control (Mohr et al., 2011). The vagus nerve is a mixed nerve composed of approximately 80% afferent fibers. It is speculated that the antidepressant effects of VNS are attributed partially to the projection of afferent fibers to the nucleus tractus solitaries (NTS), which is further connected both directly and indirectly with brain structures such as amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic regions responsible for mood and anxiety regulation (Conway et al., 2012; Conway et al., 2006; Lomarev et al., 2002; Mu et al., 2004). An animal study (He et al., 2013) has shown that stimulating the auricular branches of the vagus nerve can significantly suppress epileptiform activity via the NTS in rats, which further endorses the effect of taVNS.

More recently, brain-imaging tools have been applied to investigate the fMRI signal change evoked by VNS (Conway et al., 2013; Conway et al., 2012; Conway et al., 2006; Landau et al., 2015) and taVNS (Dietrich et al., 2008; Kraus et al., 2007; Kraus et al., 2013). In a previous study (Kraus et al., 2013), Kraus and colleagues investigated the anterior and posterior wall of the auditory canal separately. They found that stimulation of the anterior wall evoked significant limbic deactivation at the parahippocampal gyrus and the posterior cingulate cortex, as well as other regions including the thalamus, locus coeruleus, and solitary tract. In a more recent study (Fang et al., 2015), we found that after four weeks of taVNS in patients with MDD, resting state functional connectivity (rsFC) between the default mode network (DMN) and anterior insula and parahippocampus decreased while the rsFC between the DMN and precuneus and orbital prefrontal cortex increased compared

with sham taVNS. All these FC increases are also associated with HAM-D-24 score reduction. Taken together, these studies provided the neural substrates of taVNS.

We observed only a mild side effect, tinnitus, in the study, mainly due to the mistaken belief of some patients that stronger stimulation would lead to a better effect. Patients with tinnitus fully recovered after stopping the taVNS/sham taVNS without further treatment, which suggests that taVNS is a safe therapeutic method for self-administration.

There are several limitations in this study. First of all, this is not a randomized clinical trial. We used this strategy mainly due to ethical concerns. As the first study to use taVNS alone on patients suffering from mild and moderate depression without severe suicidal intent, we thought it would be wise to test the effectiveness rather than the efficacy of taVNS on the patients first. After demonstrating that taVNS can significantly reduce patients' symptoms, we recruited a second cohort of patients to test if the effect of taVNS was greater than that of the sham taVNS. Since the baseline characteristics are similar in the two cohorts of patients, we do not expect the design will influence the validity of this study. Nevertheless, a randomized clinical trial is needed in the future.

Secondly, this pilot study was single-blinded. We cannot exclude the possibility of evaluation bias, but we would like to emphasize that the scores on the self-rating scales (SDS and SAS) showed significant improvement alongside the observer-rating scales. We also applied a Pearson's correlation coefficient analysis between changes in self and observer-rating scales which showed a positive result (HAM-D-24 and SDS, $r = 0.59$ $p < 0.001$, HAM-A-17 and SAS, $r = 0.38$ $p < 0.001$). This suggests that the treatment effect of taVNS is unlikely to be due to bias and should not influence the conclusion of this study. We did not formally assess the blindness at the end of the study. However, we do believe that the device was blinded since both taVNS and sham taVNS groups experienced sensations evoked by electrical stimulation. The only difference between the two groups was the stimulation location on the ear, but patients did not know if or how the location of stimulation would affect treatment. Thus, we do not think blindness is a concern in this study.

Third, a two-week washout period might not be long enough for long-acting antidepressants. Nevertheless, since only patients with mild or moderate MDD were allowed to participate in the study, few participants took antidepressants before participating. In addition, both real and sham groups used the same washout period; we thus do not expect the short washout period would influence the results and conclusion of this study. Fourth, there is no follow up for this study although patients were allowed to continue treatment after the study ended. In our study, we found constant improvement during the 3 months over which the treatments were applied. The long-term effects of this treatment remain to be investigated. Fifth, we did not apply a multiple baseline design and start the treatment until a stable baseline had been recorded. An investigator should consider incorporating this design in a future study.

Finally, all treatments were administered by the patients themselves. We cannot be sure all patients followed the experimental protocol completely. To enhance compliance, all patients were required to complete daily entries in a diary that was checked during assessments.

Nevertheless, this self-administration method provides direct evidence toward the feasibility of widespread application of the method used within the study, which could significantly reduce treatment expenses.

In summary, we found that taVNS can significantly reduce the symptoms of depression in patients as compared to sham taVNS. Our results provide evidence for the application of this non-invasive, safe, and low cost therapeutic method for patients with mild and moderate depression.

Acknowledgments

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Highlights

- We investigated effect of real and sham taVNS in MDD patients

- taVNS produced greater improvement than sham taVNS.

- Clinical improvements evoked by taVNS continued at least 12 weeks.

- taVNS is a promising therapeutic method for MDD.

Flow Chart of the clinical trial
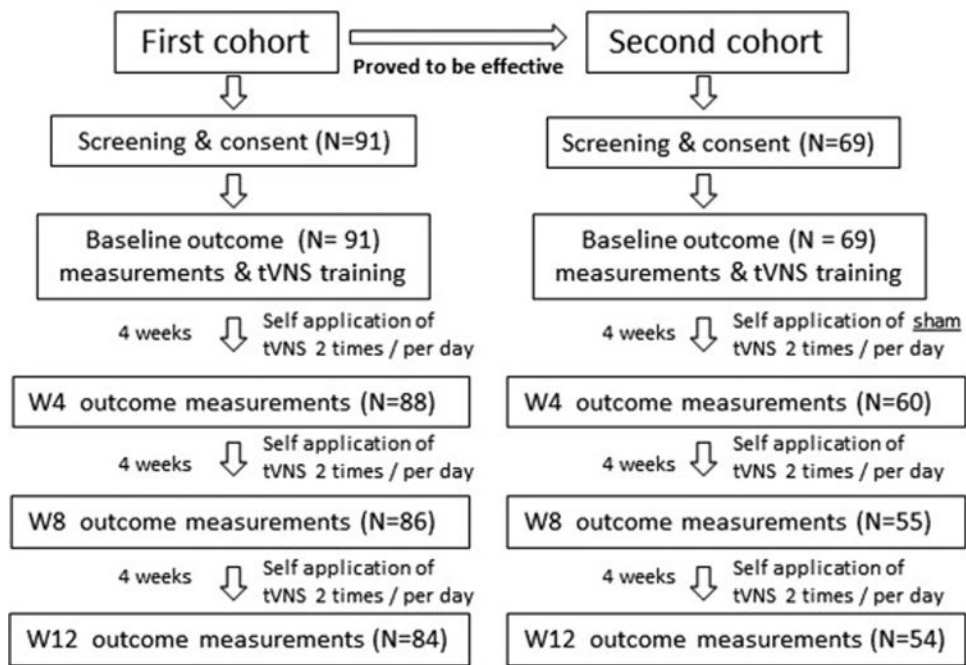
Figure 1.
The flow diagram shows detailed information regarding recruited and excluded participants.

*areas of vagus nerve innervation indicated in red

Figure 2.
Location of taVNS and sham taVNS. Red coloring indicates area with vagus nerve distribution. Red dots indicate location of taVNS; blue dots indicate the location of sham taVNS.
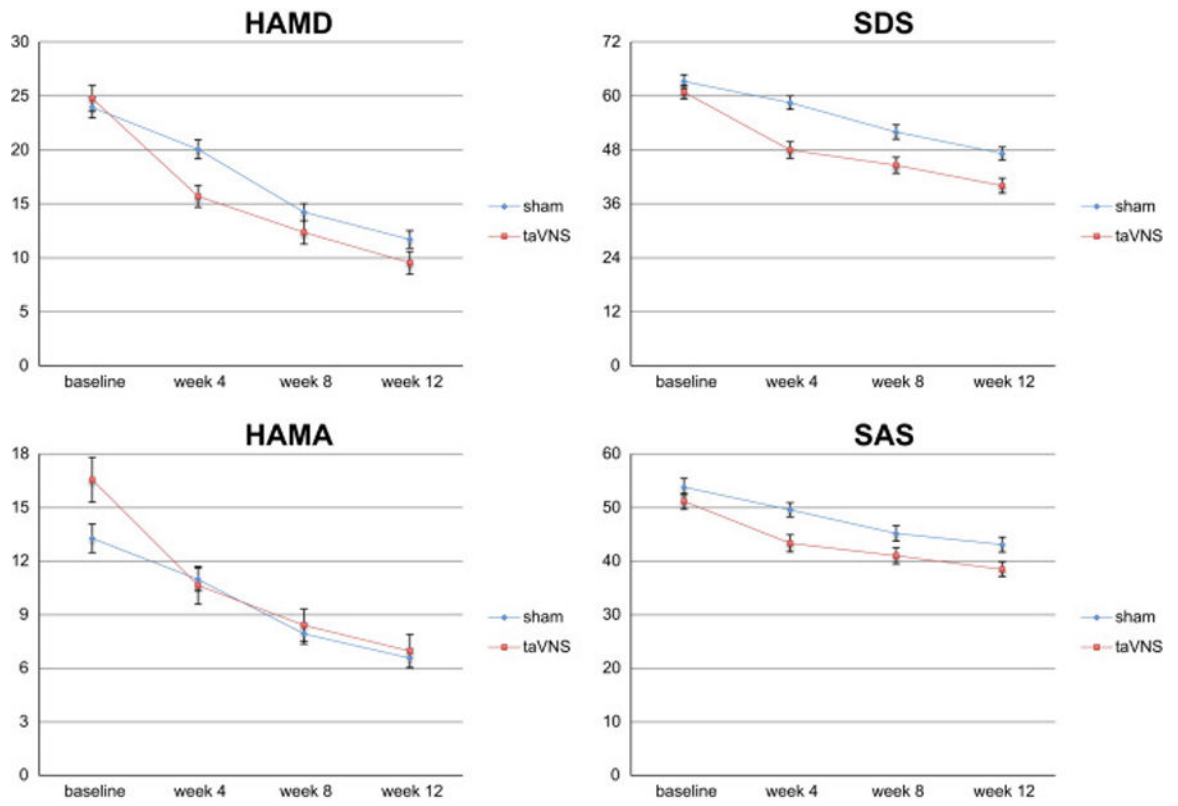
Figure 3.
Clinical outcome measurements at different time points (bars indicate 5% confidence interval).

Table 1

Baseline subjects' characteristics and clinical outcomes at baseline across two groups. All variables are presented as (mean (SD))

Group	taVNS	Sham taVNS	P value
Number	91	69	
Age	40.10(16.15)	43.88(13.95)	0.12
Gender (M/F)	23/68	20/49	0.72
Marital Status (M/S)	54/37	60/9	<0.0001
Family History (Y/N)	5/86	5/64	0.75
HAMD	25.01(7.20)	24.42(5.54)	0.52
SDS	61.68(9.29)	63.30(8.83)	0.27
HAMA	16.91(7.26)	14.16(5.09)	0.005
SAS	52.02(9.42)	52.67(9.67)	0.67

Table 2

Scores of Clinical Outcome Scales of Three Hospitals (Mean ± SD)

Time	Outcome	taVNS					Sham taVNS			
		H1	H2	H3	H1 + H2	All	H1	H2	H3	H1 + H2
Week 0	HAMD	23.3±7.0	27.6±6.2	24.6±8.8	25.1±7.0	25.0±7.2	25.1±12.4	26.8±3.8	NA	24.4±5.5
Week 4		15.1±6.2	15.4±6.5	21.5±5.6	15.2±6.3	16.0±6.5	17.9±4.9	23.3±5.1	NA	20.6±5.6
Week 8		12.3±6.4	10.7±6.0	17.3±6.8	11.7±6.2	12.3±6.5	13.0±4.2	15.7±6.2	NA	14.2±4.7
Week 12		9.8±6.1	8.0±5.4	12.7±8.3	9.1±5.9	9.5±6.3	11.0±4.1	12.6±6.9	NA	11.7±4.9
Week 0	SDS	58.0±8.5	66.7±9.1	62.3±6.5	61.6±9.7	61.7±9.3	61.5±8.8	65.4±8.4	NA	63.3±8.8
Week 4		44.6±10.5	53.5±12.2	50.4±9.4	48.3±12.0	48.5±11.8	57.8±8.3	60.4±10.0	NA	59.1±9.2
Week 8		42.2±11.0	49.0±11.8	47.4±7.5	44.8±11.7	45.1±11.3	50.0±7.2	56.6±11.4	NA	52.1±9.5
Week 12		38.8±9.6	42.1±10.1	39.0±9.6	40.2±10.1	40.1±10.0	45.3±6.8	49.5±10.1	NA	47.2±8.6
Week 0	HAMA	14.7±6.8	19.0±6.9	20.0±7.7	16.4±7.1	16.9±7.3	13.1±5.4	15.4±4.5	NA	14.2±5.1
Week 4		10.3±6.9	10.7±6.2	13.9±6.0	10.5±6.6	10.9±6.6	10.1±3.3	12.6±3.9	NA	11.3±3.8
Week 8		8.4±6.0	8.0±3.9	11.2±4.9	8.2±5.3	8.6±5.3	7.6±3.2	10.0±4.0	NA	8.7±3.8
Week 12		7.1±5.8	6.2±4.3	8.5±6.7	6.8±5.2	7.0±5.4	6.2±2.5	7.2±3.9	NA	6.6±3.1
Week 0	SAS	48.7±9.6	55.2±8.7	56.6±5.1	51.3±9.7	52.0±9.4	49.9±8.1	55.9±10.4	NA	52.7±9.7
Week 4		40.9±9.8	47.2±11.7	48.3±4.9	43.5±11.0	44.1±10.6	47.9±6.9	52.2±8.3	NA	50.0±7.9
Week 8		39.8±9.6	43.4±11.1	44.6±6.4	41.2±10.3	41.7±10.0	42.7±6.8	48.3±9.5	NA	45.2±8.5
Week 12		37.4±8.1	39.8±7.9	39.6±8.3	38.3±8.1	38.5±8.1	40.6±6.7	46.2±9.3	NA	43.1±8.4

Table 3

Comparisons of clinical outcome changes (week 0 – week 4) between taVNS and sham tsVNS groups combining hospitals 1 & 2. 95% indicates the treatment effect as indicated by outcome change between the real and sham taVNS (taVNS (pre-post) minus sham taVNS (pre-post)).

	P-value	Lower 95% CI	Upper 95% CI	Effect size
HAMD	< 0.0001	4.5	8.3	0.57
HAMA	<0.0001	1.6	5.6	0.3
SAS	0.01	0.5	7.2	0.2
SDS	<0.0001	5.5	12.4	0.44

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Table 4

Number of patients who responded (50% reduction in HAM-D-24 score) and achieved remission (defined as a HAM-D-24 scores < 8) after treatment in two groups across different time points. Please note that patients in sham taVNS shifted to taVNS after 4 weeks of sham taVNS.

	Response N (%)						Remission N (%)					
	Week 4		Week 8		Week 12		Week 4		Week 8		Week 12	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
taVNS	24 (27)	64 (73)	46 (53)	40 (47)	67 (80)	17 (20)	3 (3)	85 (97)	22 (26)	64 (74)	33 (39)	51 (61)
Sham taVNS	0 (0)	60 (100)	7 (13)	48 (87)	21 (39)	33 (61)	0 (0)	60 (100)	3 (5)	52 (95)	9 (17)	45 (83)