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Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study

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Abstract Invasive vagus nerve stimulation has been demonstrated to be an effective treatment in major depressive episodes. Recently, a novel non-invasive method of stimulating the vagus nerve on the outer canal of the ear has been proposed. In healthy subjects, a prominent fMRI BOLD signal deactivation in the limbic system was found. The present pilot study investigates the effects of this novel technique of auricular transcutaneous electric nerve stimulation in depressed patients for the first time. A total of 37 patients suffering from major depression were included in two randomized sham controlled add-on studies. Patients were stimulated five times a week on a daily basis for the duration of 2 weeks. On days 0 and 14, the Hamilton Depression Rating Scale (HAMD) and the Beck Depression Inventory (BDI) were assessed. In contrast to sham-treated patients, electrically stimulated persons showed a significantly better outcome in the BDI. Mean decrease in the active treatment group was 12.6 (SD 6.0) points compared to 4.4 (SD 9.9) points in the sham group. HAMD score did not change significantly in the two groups. An antidepressant effect of a new transcutaneous auricular nerve stimulation technique has been shown for the first time in this controlled pilot study. Regarding the limitations of psychometric testing, the risk of unblinding for technical reasons, and the small sample size, further studies are necessary to confirm the present results and verify the practicability of tVNS in clinical fields.

Keywords Transcutaneous · Auricular nerve stimulation · tVNS · TENS · Depression · Psychiatric

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Introduction

Major depressive disorder is a disease with prominent individual, medical and economic impacts (Kessler et al. 2010; Shern and Moran 2009; Stegmann et al. 2010). A relevant proportion of patients suffering from a therapy-resistant depressive disorder are increasingly being treated with brain stimulation techniques (Bewernick et al. 2010; Shelton et al. 2010) (for a review see Marangell et al. 2007). One of these interventions is vagus nerve stimulation, which has been tested in a number of clinical trials (Daban et al. 2008; Sackeim et al. 2001). Although the acute and long-term efficacy of vagus nerve stimulation is still under debate, VNS was associated with a significant reduction of depressive symptoms in the short and long term in the majority of the studies available (Daban et al. 2008).

A main systematic problem is that research on invasive brain stimulation techniques is restricted to treatment resistant depression. Outcome data would probably be much better if typical depressed patients were included in the studies, as we know from electro-convulsive therapy (ECT), also typically indicated in treatment resistant depression (Avery and Winokur 1977).

Recently, a novel method has been described to non-invasively stimulate brain structures in a similar way to vagus nerve stimulation (Fallgatter et al. 2003, 2005; Ventureyra 2000). The authors called the new method

transcutaneous vagus nerve stimulation (tVNS). The method is based on the well-known technique of transcutaneous electrical nerve stimulation (TENS), which is used in acute and chronic pain syndromes (Lampl et al. 1998). Moreover, mild effects on mood and cognition have been found in elderly subjects (Scherder et al. 2000; Luijpen et al. 2004). TENS was applied by fixing electrode pads to the skin on the subjects' backs. However, no data are available on applying the TENS method in depressed patients within the outer canal of the ear to stimulate a specific area called Rhamsay-Hunt's zone, as described by Ventureyra and Fallgatter (Fallgatter et al. 2003, 2005; Ventureyra 2000). Recently, fMRI studies have shown marked changes of the BOLD signal in limbic and possibly brain stem areas during transcutaneous electrical nerve stimulation in the left outer auditory canal (Dietrich et al. 2008; Kraus et al. 2007). Psychophysical experiments showed mood enhancing effects during tVNS in healthy subjects and no adverse side effects (Kraus et al. 2007). Antidepressant effects have not been shown to date. The present study is the first randomized study using the new method in depressed patients admitted to a psychiatric hospital. It is hypothesized that auricular TENS as an add-on treatment to a standard therapy will show antidepressant effects. The feasibility of a novel non-invasive treatment option is to be evaluated.

Materials and methods

General procedure

The trial was designed as a randomized controlled pilot study using a new technique as an add-on to standard treatment for patients suffering from a major depressive episode according to ICD-10 (World Health Organization 1992) and DSM-IV (American Psychiatric Association 2000). After hospital admission, patients underwent a 1- to 2-week period of clinical diagnostics and initiation of a standard antidepressant therapy (see Table 1) combined with cognitive behavioural therapy.

All participants were carefully screened to rule out the existence of inflammatory, cardiac, endocrine, renal and hepatic disease by means of a structured medical history, physical examination, routine laboratory testing, and ECG. Patients were excluded if co-morbidity of alcohol or drug dependence was detected.

Subjects gave their written informed consent and were instructed that they could withdraw from the experiment at any time. The study was approved by the responsible ethics committee of the German Regional Association of Physicians (Landesärztekammer) in Munich, Bavaria. Before the experiment, subjects were made familiar with the stimulation procedures and the experimental protocols.

Stimulation lasted 15 min once (study 1) or twice a day (study 2) for the duration of 2 weeks on 5 days each week.

Before and after stimulation sessions, patients were scored on the Hamilton Depression Rating Scale (HAMD, Hamilton 1960). Patients were asked to fill in questionnaires of Beck's Depression Inventory (BDI, Beck et al. 1961). There were no differences in baseline values between the compared groups concerning HAMD and BDI scores (*t* test).

For statistical calculations, the software XLSTAT Version 2009.2.02 (Addinsoft^{TM}) was used. Pre-post comparisons were statistically performed by Student's *t* tests, differences of changes during treatment course were compared by Mann–Whitney *U* tests. After completing the study, all subjects were asked to speculate whether they had been part of the auricular TENS or the sham group.

Study 1

Twenty-two patients were included in a first trial. Subjects were randomized alternately to auricular TENS (11 persons) or sham stimulation (11 persons). Groups did not differ either with regard to distribution of sex and type of depression (single episode or recurrent disorder; both n.s. after χ^2 test) or with regard to age, duration of current episode, and total years from first onset of disease (n.s. after Mann–Whitney *U* test; see Table 1).

For applying electrical stimuli, the TENS microstimulator unit NET-2000 made by Auri-Stim Medical, Inc., 11172 Huron St. Suite 22, Denver, CO, USA, was used. This unit is available on the US market and was approved by the FDA in 2006 (Regulation Number: 21 CFR 882-5800). A CE conformity certificate has been granted for the European market. NET-1000 and NET-2000 devices were labelled as nerve stimulators and were classified as Class IIa, low-risk medical devices. The control unit of the investigator is battery powered and patients use a head set with electrodes placed in both outer ears (see Fig. 1). On both sides, four electrodes were placed crosswise, each with a diameter of about 3 mm. The investigator could choose various parameters like intensity (0–600 mA), frequency (0.5–100 Hz), and adding a sound during the stimulation.

Electrical stimuli of 1.5 Hz unipolar rectangle waves were applied. To find out the optimum strength of current, stimulus intensity was adjusted in small steps from 0 μA to maximum 600 μA. Before each experiment, the individual thresholds of perception and of pain were determined for each subject. The threshold of perception meant that the stimulus was just noticeable, the threshold of pain meant that the subject experienced the onset of a painful

Table 1 Subjects' characteristics; groups did not differ significantly as tested for all given variables, except for profession and medication

Gender	Age	Duration of current episode (months)	Single/recurrent episode	Total years since first onset	Educational level	Profession	Medication
Study 1 ($N = 22$)							
tVNS (11)							
f	51	1	r	5	n.a.	Non-skilled worker	Dul
f	42	1	r	2	a	Employee	Ven, Pre
m	58	0	r	27	a	Retired	Dox, Lit, Mir, Ven
f	49	3	r	20	n.a.	Employee	Esc
m	31	1	r	2	a	Unemployed	Esc, Car, Que
m	40	12	s	1	a	Employee	Mir
m	39	3	r	8	a	Unemployed	Cit
f	48	3	r	11	n.a.	Unemployed	Esc, Que
f	68	1	r	42	n.a.	Retired	Esc, Mir
m	27	3	s	0	n.a.	Employee	None
m	43	6	r	3	n.a.	Employee	Dul, Que
Sham (11)							
f	48	2	r	12	n.a.	Non-skilled worker	Ven, Que, Pre
m	41	1	s	0	n.a.	n.a.	Bup
f	30	1	r	4	a	Unemployed	Ven, Mir, Que
f	48	n.a.	s	n.a.	a	Employee	Ven, Que, Pre
f	77	1	r	4	n.a.	Unemployed	Gal, Dul, Que
f	47	24	r	28	a	Retired	Dul
f	44	1	r	2	a	Unemployed	Ven, Pre
m	39	1	r	8	a	Self-employed	Cit
m	42	1	s	0	a	Employee	Fluo, Mir
f	40	6	s	0	a	Retired	Esc
f	56	1	r	1	a	Unemployed	Dul, Pre
Study 2 ($N = 15$)							
tVNS (7)							
f	47	2	r	13	n.a.	Retired	Ago
f	57	4	s	0	a	Employee	Ven, Pre
f	41	2	r	3	a	Manager	Cit
f	59	3	s	0	n.a.	Unemployed	Mir, Que, Ven
f	44	1	s	0	n.a.	Unemployed	Fluo
f	53	2	r	17	a	Employee	Ven
m	40	1	r	1	a	Employee	Dul, Pre
Sham (8)							
f	49	2	r	2	a	Employee	Esc, Pre, Bup
m	58	6	s	0	a	Employee	Cit
m	47	3	r	7	a	Retired	Cit, Mir
m	45	7	r	3	n.a.	Unemployed	Pre
f	59	4	r	20	n.a.	Unemployed	Ven, Tri, Bus
f	51	1	r	4	a	Self-employed	Que, Esc
m	45	1	s	0	n.a.	Employee	Cit
m	26	2	s	0	a	Employee	Esc

For details, see "Materials and methods"

a apprenticeship, *n.a.* not available, *Dul* duloxetine, *Ven* venlafaxine, *Pre* pregabalin, *Dox* doxepin, *Lit* lithium, *Mir* mirtazapine, *Esc* escitalopram, *Car* carbamazepine, *Que* quetiapine, *Cit* citalopram, *Bup* bupropion, *Fluo* fluoxetine, *Ago* agomelatine, *Tri* trimipramine, *Bus* buspirone

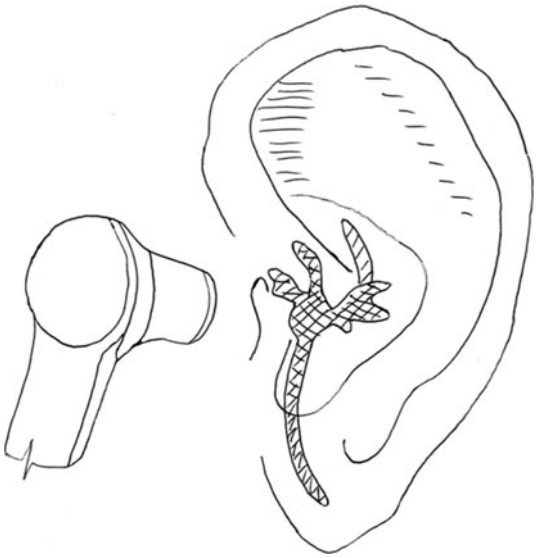

Fig. 1 Principle of transcutaneously stimulating fibres of Ramus auricularis nervi vagi by electrodes in the outer ear

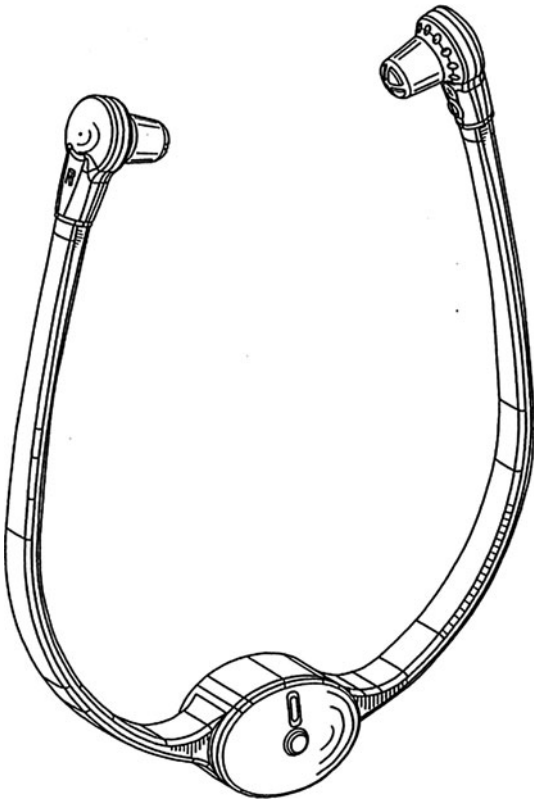

Fig. 2 NET-1000 unit by Auri-Stim Medical, Inc., approved by the FDA in 1998. Intensity of rectangle pulses is fixed at 130 μA by Auri-Stim Medical, Inc

sensation. Subjects of the active treatment group were then stimulated with an intensity just below the individual threshold of perception. In the sham group, no current at all was applied, the clamps having been unplugged. Both the auricular TENS patients and the sham-treated patients were exposed to the same sort and intensity of sound patterns generated from the control unit. Neither the auricular TENS patients nor the sham-treated patients experienced current sensations during the experiments. Like a sensitization phenomenon, three patients of the auricular TENS group reported a low sensation of current about 5 min after beginning the stimulation. In these cases, the intensity of current was immediately reduced to a subthreshold level. Afterwards, these three patients did not differ concerning the results of psychometric ratings compared to the eight other subjects of the active treatment group.

Study 2

Fifteen patients suffering from a major depressive episode were included in a second study. Six patients were stimulated once a day (in 2009) and nine patients were stimulated twice a day (in 2010). Groups did not differ either with regard to distribution of sex and type of depression (single episode or recurrent disorder; both n.s. after χ^2 test) or with regard to age, duration of current episode, and total years from first onset of disease (n.s. after Mann–Whitney *U* test; see Table 1).

In study 2, the easier to handle device NET-1000 (self-application by the patients) also made by Auri-Stim Medical, Inc. was used (see above, and Fig. 2). In this device, the stimulus generating unit and the battery are already integrated into the clamp itself. A wired extra box is obsolete. Stimulation parameters are fixed, intensity of current is 130 μA, frequency is 1.5 Hz. Thus, due to the generally low intensity of current, all patients were stimulated on a subthreshold level. The sham-treated patients received a manipulated clamp in which the wires that conduct the stimulation current had been disconnected. The accompanying sound was not switched off either in the auricular TENS group or in the sham group.

All other criteria and procedures were the same as in study 1.

None of the authors have any financial interest in the procedures described in the text, in particular, using the devices NET-1000 and NET-2000.

Results

In study 1, Beck Depression Inventory (BDI) self-rating scores during auricular TENS decreased from 27.0 to 14.0 ($t = 6.2$, $p < 0.000$), while the sham-stimulated patients did not show significant reductions in the BDI (31.0–25.8 points, $t = 1.4$, n.s.). In study 2, the change is very similar (29.4–17.4 points, $t = 6.3$, $p < 0.05$) concerning auricular

TENS, and no significant difference could be detected in the sham group (28.6–25.4, $t = 1.3$, n.s.). The pooled data ($N = 37$) show a significant reduction of BDI self-rating scale from 27.9 to 15.3 points ($t = 8.7$, $p < 0.0001$), while sham-treated patients experienced no significant change (30.0–25.6, $t = 1.9$, n.s.) (Fig. 3).

Differences of changes of BDI scores during auricular TENS compared to sham stimulations were significant ($U = 265.0$, $p = 0.004$). For details, see Table 2.

Mean HAMD scores significantly decreased in both the auricular TENS group (16.6–11.2, $t = 3.9$, $p = 0.001$, $N = 37$) and the sham group (18.1–11.5, $t = 3.9$, $p = 0.001$, $N = 37$). There was no significant difference between the two groups concerning changes of HAMD scores ($U = 161.1$, n.s.). For details, see Table 2.

After completing study 1, patients were asked to speculate whether they had received stimulation or not. All participants of the auricular TENS group believed that they really had been stimulated, compared with 60 % of those in the sham group.

After completing study 2, all auricular TENS group members believed that they really had been stimulated, compared with 70 % of those in the sham group.

Heart rate, blood pressure, and blood values did not change over the course of treatment (data not shown). Subjects did not report any unpleasant sensations during or after the stimulation procedures. No local skin irritations or unpleasant acoustic or vestibular reactions were observed. No adverse side effects were observed or reported after the trial.

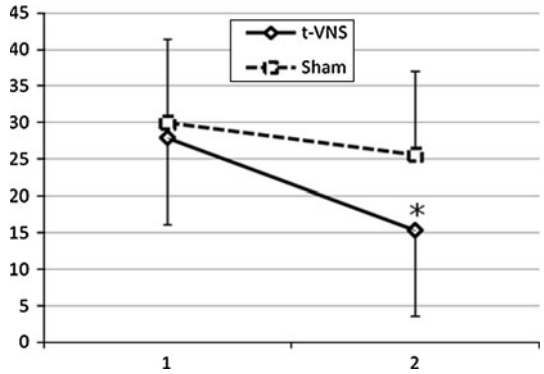

Fig. 3 Change of Beck Depression Inventory (BDI) scores during tVNS compared to sham stimulation; *1* baseline, *2* after 2 weeks of treatment, $*p < 0.05$

Discussion

This is the first randomized study using the novel non-invasive auricular TENS technique in depressed patients. Transcutaneous electrical nerve stimulation was applied as an add-on to a standard inpatient treatment. The antidepressant effect as measured by the BDI was very prominent: Patients treated with auricular TENS gained 12.6 (SD 6.0) points, compared to 4.4 (SD 9.9) points of the sham-stimulated patients. Hence, the self rating scale shows subjective symptom amelioration in depressed patients of almost 50 % (47 %). This represents the typical response criteria in therapy studies. The additional antidepressant effect appears to be similar to other non-invasive brain stimulation techniques. Two weeks of repetitive transcranial magnetic stimulation (rTMS) led to a BDI reduction from 29.2 to 18.3 points (Fitzgerald et al. 2006).

Table 2 Change of Beck Depression Inventory (BDI) scores during tVNS compared to sham stimulation over 2 weeks

Study ($N = 37$) Mean SD	HAMD Pre	HAMD Post	HAMD Difference	BDI Pre	BDI Post	BDI Difference
1 ($N = 22$)						
tVNS (11)	15.4	10.6	−4.8	27.0	14.0	−13.0#
	6.8	5.7	6.5	12.8	9.5	6.7
Sham (11)	20.1	12.9	−7.2	31.0	25.8	−5.2
	6.9	7.9	8.1	10.1	14.1	11.7
2 ($N = 15$)						
tVNS (7)	18.4	12.1	−6.3	29.4	17.4	−12.0*
	6.3	6.0	4.0	9.9	9.6	4.7
Sham (8)	15.3	9.6	−5.9	28.6	25.4	−3.2
	8.0	3.6	5.2	12.7	14.2	6.4
1 + 2 ($N = 37$)						
tVNS (18)	16.6	11.2	−5.4	27.9	15.3	−12.6*
	6.8	5.9	5.7	11.8	9.7	6.0
Sham (19)	18.1	11.5	−6.6	30.0	25.6	−4.4
	7.8	6.7	7.1	11.4	14.2	9.9

* Significant difference between tVNS and sham stimulation, $p < 0.05$ in Mann–Whitney U test

$p = 0.057$ in Mann–Whitney U test

In comparable add-on studies of rTMS (Fitzgerald et al. 2006; Frank et al. 2010), effects are similar (for a review see Daskalakis et al. 2008). Moreover, other non-invasive methods of brain stimulation, such as transcranial direct current stimulation (tDCS), may be less effective than the presented auricular TENS method, leading to a BDI reduction from 27.8 to 21.9 points (Loo et al. 2010).

Interestingly, the easier-to-use Net-1000 device, which can be applied by the patients themselves, seems to be as effective as the more sophisticated model NET-2000, which necessitates a physician to set the individually best parameters in each session. However, it must be taken into consideration that subjects who used NET-2000 were stimulated only once a day. Although higher intensity rates can be applied with the Net-2000, effectiveness did not differ in comparison to the NET-1000, at least in the present pilot study. If the results of the present study can be replicated, a new device may be available to depression therapy, comprising a very easy form of auricular TENS using NET-1000 on a large scale.

Finally, it remains unclear whether the present auricular TENS method really is a form of vagus nerve stimulation. It has to be discussed whether the electrical stimulation in the outer ear might be an unspecific one. Effects may be mediated via the trigeminal nerve or the glossopharyngeal nerve. Yet, several studies of basic research do provide evidence that it is possible to stimulate auricular cutaneous vagal fibers, leading to central nervous system activations (Berthoud and Neuhuber 2000). Electrophysiological studies using evoked potentials showed brain stem reactions by stimulating vagal afferences in the left outer ear (Fallgatter et al. 2003, 2005; Polak et al. 2007, 2009a, b). Moreover, two different fMRI studies demonstrated BOLD signal activations in limbic brain areas (Dietrich et al. 2008; Kraus et al. 2007). Altogether, it seems not to be very likely that the demonstrated effects are only of an unspecific nature (Greif et al. 2002; Bystritsky et al. 2008). Rather, the effects are similar to those of invasive vagus nerve stimulation—a well-examined invasive method in neurology and increasingly in psychiatry (Bajbouj et al. 2010; Schlaepfer et al. 2008; Zobel et al. 2005).

Limitations

Scores of the Hamilton Depression Rating Scale (HAMD) did not differ between the two groups. Thus, in contrast to patients' self-ratings, the external ratings were not significantly different after 2 weeks of stimulation. However, a period of observation of only 14 days in hospitalized depressed patients seems to be rather short, especially, because the stimulation regime was used in addition to standard treatment including antidepressants and psychotherapy. Unblinding effects also have to be considered, because it could not be completely excluded that patients had sensations during electrical stimulation. Therefore, tVNS patients might have noticed that they were in the study group, and sham-treated patients might have believed that they were in the placebo group if sensing nothing. The interview of the participants after each study session as to whether they believed they had been stimulated did not produce absolutely consistent results. A major limiting factor is that little data are available describing the precise function of each of the stimulation devices. In general, a better sham/placebo condition needs to be found. Furthermore, the case number was rather small in this pilot study. Thus, the experimental groups were a little too inhomogeneous with regard to the study parameters. Subgroups could not be formed without losing statistical power. The risk to significant results would be minimized using a bigger sample of more homogeneous study participants. On the other hand, the naturalistic design of the present study is one of its strong points. However, future auricular TENS trials should include larger patient samples, and ideally should be performed as controlled multicentre trials.

Conclusion

In this controlled pilot study, an antidepressant effect—at least in the subjects' view of the BDI—of a non-invasive auricular electrical nerve stimulation could be shown for the first time. In addition, further data have been provided to support the hypothesis of the feasibility of transcutaneous vagus nerve stimulation. For the future, a larger number of patients will have to be investigated, as far as possible within multicentre studies, to verify the efficacy and safety of the new method. Then, in particular, the focus should be directed towards long-term effects of this method.

Non-invasive vagus nerve stimulation may also be helpful not only as a last resort treatment like invasive VNS in patients suffering from therapy-resistant major depressive episode, but also as an alternative option in a broader range of psychiatric treatment regimens.

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