LETTER TO THE EDITOR

USE OF BIOPHYSICAL TREATMENT FOR THE MANAGEMENT OF MILD ANXIETY, DEPRESSION AND STRESS: A RANDOMIZED CONTROLLED TRIAL

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To the Editor,

Depression, anxiety and stress significantly affect both personal and public health (1), either as a primary psychological complaint or as an additional burden component of most physical chronic diseases. The effective management of early stages of depression, anxiety and stress still represents a frequent unmet medical need considering the aging population, increased number of co-morbid diseases and the need for personalized treatments (2).

Biophysical treatments can exert their clinical effect through a resonance effect of their therapeutically delivered electromagnetic signals (either endogenous or exogenous) to target tissues, organs, and/or the entire organism (3). To date, biophysical therapeutic methods have emerged as integrative tools in a wide range of clinical settings such as pain, psoriasis and chronic kidney disease (4). Preliminary evidence shows that minor anxiety and depression symptoms can also be significantly reduced after biophysical treatments (5). Furthermore, we recently conducted a pilot study involving twenty-four patients with mild anxiety/stress symptoms (Generalized Anxiety Disorder 7-item scale of > 5) randomized to biophysical treatment (N = 12) or placebo control (N = 12) (6). After 1 month of biophysical therapy, we observed a significant reduction all Depression Anxiety Stress Scale (DASS)-21 questionnaire subscales; depression, anxiety and stress compared to placebo control. The aim of this clinical trial is to extend and confirm these findings in a larger sample size (N=100) over a period of three months.

MATERIALS AND METHODS

Patient recruitment and study design

This was a randomized controlled trial (the protocol was not registered for this trial) and included patients presenting with mild anxiety symptoms and related symptoms of depression and stress. The recruitment of participants was carried out by physicians and included patients attending the Poliambulatorio San Marco in Palmanova, Italy from January 2018 to June 2018 who completed a Generalized Anxiety Disorder 7-item scale (GAD-7) (7) prior to psychiatric consultation.

Inclusion criteria were: a score >5 for the Generalized Anxiety Disorder 7-item scale (GAD-7) (7); (i) presence of anxiety symptoms; (ii) age between

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18 and 70 years; (iii) fluent Italian speaker; (iv) legal capacity to consent to the treatment; (v) no psychotropic medication use throughout the study. Exclusion criteria were: (i) presence of severe psychiatric disorders; (ii) cognitive disorders such as overt dementia; (iii) drug or alcohol abuse; (iv) suicide attempts; (v) current pregnancy.

The research protocol was proposed to patients who met the inclusion criteria, with an explanation of the aims of the study and declaring the possibility that they would be assigned by random allocation to the experimental group (biophysical therapy) or the control (placebo) group. After being informed about the aim, methods and timing of the study, all patients provided a signed written informed consent form. This study was performed in accordance with the declaration of Helsinki. Psychological/psychiatric assessment (using questionnaires) was performed at baseline (before the first session of biophysical treatment) and again at the end of treatment (after 3 months).

The patients were randomly assigned to the experimental or the control group with a 1:1 ratio (50 in the intervention and 50 in the control group). To ensure allocation concealment, the sequence was determined by an independent researcher blind to the initial assessment, using a random number generator (www.randomizer.org). To ensure the blinding of the clinical psychologists performing the assessments, the study coordinator communicated the treatment assignment to each patient.

Biophysical therapy

This study was single-blind: patients were not aware which group of treatment they would be assigned to. The treatment procedure was the same for the experimental and the control group. The experimental group was treated with biophysical therapy using the Med Select 729 device (Wegamed, GmbH, Essen, Germany) the methodology of which has been previously described in detail (4). This medical device operates in a low frequency range (between 0 and 20 kHz) using a magnetic field intensity similar to the Earth's magnetic field with a maximum of 50 μT. It allowed us to record input signals using two electrodes and to send output signals to the patient through a magnetic carpet where the patient can lie down (in this way the entire body of the patient can be treated).

The biophysical therapy protocol comprises three steps. The purpose of this sequence is to restore the systemic self-regulation capacity, restore the relaxation capacity, and restore the autonomic regulation; it allows to carry out both the treatment and to record it on the aqueous system simultaneously. i) The first phase is the ''regulation therapy'' program selected on the touch-screen of Med Select 729 device (Wegamed, GmbH, Essen, Germany) to record the endogenous electromagnetic input signals using two electrodes placed on the forehead of each patient and for delivering the therapeutic electromagnetic output signals (a simultaneous combination of the patient's own signals with the carrying and modulating ones) through a magnetic carpet on which the patient lies for 6 minutes. This program has a fixed carrier frequency of 32 Hertz, a modulation frequency oscillating between 7 and 12 Hz, and 12.5-μT magnetic field strength. The patient's own signals delivered simultaneously with those of the carrier and the modulating supplied by the equipment has both a general purpose of entrainment and a specific individual self-regulation. ii) The ''relaxation therapy'' program is then selected from the Med Select 729 device touch-screen to record the endogenous input signals using two electrodes placed on the forehead for delivering the therapeutic output signals of a magnetic carpet on which the patient lies on for 10 minutes. This program has a fixed carrier frequency of 7 Hz, a modulation frequency oscillating between 4 and 10 Hz, and 17.5-μT magnetic field strength. iii) The third phase of treatment involves the "autonomic therapy" selected from the Med Select 729 device touch-screen to record the endogenous input signals using two electrodes positioned on the forehead for delivering the therapeutic output signals of a magnetic carpet on which the patient lies on for 12 minutes. This program has a variable carrier frequency of one-minute recurring sequences at 8-12-50-8-95-275 Hz, a fixed modulation frequency at 10 Hz, and 50-μT magnetic field strength.

During these three steps, the therapeutic output signals were simultaneously recorded on an aqueous

system commercially available (Nomabit Base, Named SRL, Italy MB) by placing the solution in an appropriate output coil, incorporated for this purpose in Med Select device 729. Patients self-administered the aqueous solution Nomabit Base daily in order to allow the therapeutic information recorded to be taken once a day for 3 months. The control group is the placebo group, which received placebo treatment following the same procedures as the experimental group without the recording and subsequent administration of the therapeutic signals. This group received Nomabit Base solution as a placebo, without any signal recorded. The control group received the treatment for 3 months.

Data collection

In addition to a module on demographic data, the following psychological self-report questionnaires were administered at baseline and after 3 months by the physician, independent of the research protocol and blinded to treatment group, using the same timing and tools in both groups.

Each patient was requested to complete the self-rating DASS-21 questionnaire (8). The DASS-21 is a self-administered questionnaire using a set of three self-report scales designed to measure the emotional states of depression, anxiety and stress. Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The depression scale

Table I. *Baseline clinical characteristics of control and biophysical treatment groups*

Charactersitic	Control (N=50)	Biophysical (N=50)	P-value
Age, years (mean±SD)	46.62±10.81	47.04±13.92	0.867
Females, n (%)	41 (82.0)	42 (84.0)	1.000
Education (mean±SD)	12.40±2.97	12.76±3.65	0.590
Employment, n (%)			0.417
Employed	34 (68.0)	28 (56.0)	
Retired	1 (2.0)	1 (2.0)	
Student	2 (4.0)	6 (12.0)	
Unemployed	13 (26.0)	15 (30.0)	
Marital Status, n (%)			0.037
Divorced	1 (2.0)	8 (16.0)	
Married	37 (74.0)	27 (54.0)	
Single	11 (22.0)	14 (28.0)	
Widowed	1 (2.0)	1 (2.0)	
Baseline assessment (median [IQR])			
DASS Depression	16.00 [8.50, 22.00]	15.00 [10.00, 20.00]	0.833
DASS Anxiety	10.00 [4.00, 18.00]	10.00 [6.00, 18.00]	0.854
DASS Stress	20.00 [14.00, 28.00]	22.00 [16.50, 27.50]	0.830
CES-D	21.50 [16.25, 30.75]	24.50 [19.00, 28.00]	0.622
WHO Enviromental	59.50 [50.00, 67.50]	63.00 [50.00, 67.50]	0.989
WHO physical	44.00 [38.00, 50.00]	44.00 [38.00, 50.00]	0.445
WHO psychological	47.00 [44.00, 56.00]	50.00 [44.00, 56.00]	0.682
WHO social	56.00 [31.00, 73.50]	56.00 [26.50, 69.00]	0.648

Data are presented as mean ± standard deviation or number and percent or median and inter quartile range (IQR). CES-D = Center for Epidemiologic Studies Depression Scale Revised. Statistical significance is represented by p values for comparison of variables in control and biophysical groups. DASS-21 = Depression Anxiety Stress Scale.

assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious effect. The stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items.

The Center for Epidemiologic Studies Depression Scale Revised (CES-D) is a self-assessment scale of 20 items rated on a 4-point Likert scale (0 = never or rarely, 3 = most of the time) to measure the presence and severity of depressive symptoms (9).

WHO-QOL-BREF is a measure to assess the Quality of Life that consists of 36 items, divided into four domains (physical health, psychological health, social relationships health, and environmental health) and rated on a 5-point Likert scale (0 = not at all, 5 = completely) (10).

Statistical analysis

Continuous variables are presented using mean or median as a measure of centrality and standard deviation or interquartile range as a measure of variability as appropriate according to the Shapiro–Wilk normality test. Differences in socio-demographic and baseline clinical characteristics between the groups were assessed using Mann–Whitney test for continuous variables and χ^2 or Fisher's test as appropriate, for categorical measures. Linear mixed model approach was used to analyse the pre-post intervention effect considering interaction between time and groups and adjustment for unbalanced variables. The linear mixed model was evaluated under REML (reduced maximum likelihood) estimation. The sample size computation was based on ANOVA analysis with two repeated measures and within-between interactions. Considering a medium effect size (Cohen's f = 0.25) on primary outcome CES-D, a total of N=50 patients would allow us to achieve a power of 0.93, with type I error equal to 0.05. All tests were two-tailed and a p-value of <0.05 was considered statistically significant. P-value adjustment for post-hoc test was applied. All analyses were carried out using R version 3.6.1.

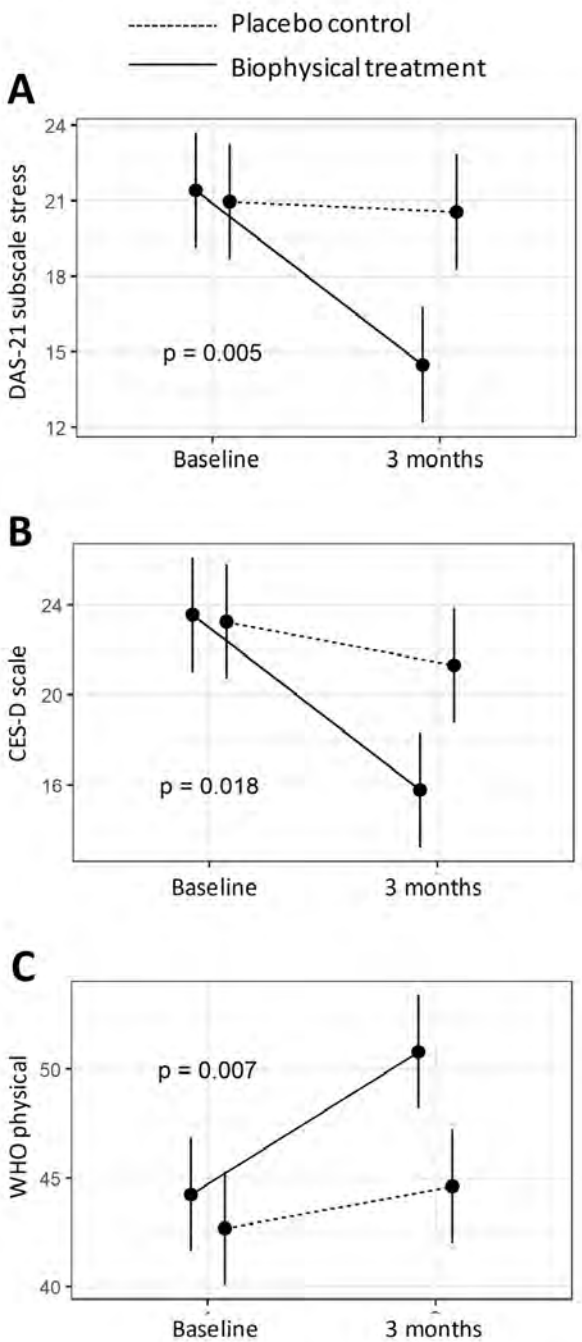

Fig. 1. *Effect of biophysical therapy and placebo control on DASS-21 subscale stress, CES-D and WHO physical. Data are presented as mean ± SD and p-values denote statistical significance between groups at 3 months.*

RESULTS

Baseline clinical and demographic characteristics

A total of 100 subjects were included in the study, 50 (mean age: 47.04±13.92 years) in the biophysical therapy group and 50 (mean age: 46.62±10.81 years) in the control group. After completion of the Generalized Anxiety Disorder 7-item scale (GAD-7) questionnaire, physicians only included patients having a GAD-7 score of >5, defined as having mild anxiety/depressive symptoms. Clinical characteristics and depression/anxiety and stress assessment for control and biophysical patient groups are presented in Table I. The majority of patients were female (83%) and 62% of patients were currently employed. A higher proportion of patients were married in the control group and divorced in the biophysical group this difference just attaining statistical significance compared to the biophysical group (p=0.037). All other baseline measures of depression, anxiety, stress (DASS-21 subscales), depression (CES D scale) and WHO QoL scales related to physical, psychological, social and environmental were similar for the two groups (Table I).

Effect of biophysical treatment on DASS-21 subscales and WHO QoL subscales

In patients who were assigned biophysical therapy, a reduction in all DASS-21 subscales was observed, with statistical significance only observed for the stress subscale. From baseline to the 3-month follow-up, biophysical-treated patients had a -6.92 points decrease in DASS stress score (p=0.005, Fig. IA), while control patients had a non-significant improvement. After 3 months, control and biophysical patients' mean scores were 18.62 and 12.86, respectively (difference of 5.75, 95% CI: 1.36; 10.15, p=0.005, Table II).

A statistically significant decrease was also observed for CES-D scale in biophysical treated patients compared to controls after 3 months' follow-up; depression score (CES D scale) decreased by -7.78 points (p=0.018, Fig. IB) compared to -1.94, in control patients. After 3 months, control and intervention patients' mean scores were 21.19 and 15.54, respectively (difference of 5.64, 95% CI: 0.70; 10.59, p=0.018, Table II).

For WHO QoL outcome measures only WHO physical QoL significantly improved over 3 months (5.74 mean increase, p=0.007, Fig. IC) in the biophysical group. After 3 months, control and biophysical patients' mean scores were 50.32 and 44.58. respectively (difference of 5.74, 95% CI: 0.78; 10.70, p=0.007) (Table II). Depression and anxiety (DASS-21 subscales), WHO psychological, social and environmental QoL improved to a greater extent in the biophysical group compared to controls, however the difference did not attain statistical

Table II. *Change in mean scores for DASS-21 outcome and WHO QoL measures in control and biophysical treatment groups after 3 months*

	Biophysical group	Control	Difference (95% CI)
DASS-21 depression	6.2 (3.56;8.84)	2.04 (-0.60; 4.68)	4.08 (-0.33; 8.49)
DASS-21 anxiety	4.88 (2.27; 7.49)	-0.12 (-2.73; 2.49)	4.45 (-0.06; 8.96)
DASS-21 stress	6.92 (3.74; 10.10)	0.4 (-2.78; 3.58)	5.75 (1.36; 10.15)
CES-D	7.78 (4.85;10.71)	1.94 (-0.99; 4.87)	5.64 (0.7; 10.59)
WHO physical	-6.56 (-9.80; -3.32)	-1.94 (-5.18; 1.30)	5.74 (0.78; 10.70)
WHO psychological	-6.11 (-9.49; 2.73)	-2.60 (-5.95; 0.75)	4.14 (-1.18; 9.48)
WHO social	-6.98 (-14.64; 0.68)	-2.02 (-9.68; 5.64)	2.02 (-11.11; 15.16)
WHO environmental	-4.8 (-7.85; 1.75)	-2.62 (-5.67; 0.43)	2.06 (-4.41; 8.52)

significance when comparing mean scores at 3 months (Table II). Statistical significance between the control and the biophysical groups were adjusted for marital status.

DISCUSSION

The present clinical trial confirms results of a recent pilot study involving twenty-four patients with mild anxiety/stress symptoms (6) and extends them further by using a larger sample size (N=100) and longer treatment period (three months). Patients presenting with mild anxiety/depression can experience a significant reduction in these symptoms as early as 3 months after biophysical therapy. Both DASS-21 subscales and WHO QoL measures were improved following treatment with biophysical therapy for 3 months compared to untreated controls. To the best of our knowledge, this is the first study to investigate the feasibility and effectiveness of using biophysical therapy to treat mild-to-moderate levels of psychological distress. Moreover, this study sheds light on an integrative/unconventional therapeutic option for the treatment of mild-to-moderate depressive symptoms. According to clinical guidelines, possible first treatments for mild-to-moderate depression include self-help programme, computerised cognitive behavioural therapy and physical activity exercise (11). Further treatment options are represented by antidepressant or psychological treatments. Therefore, if further studies confirm its efficacy, biophysical therapy could represent an additional treatment available to general practitioners or other healthcare professionals to intervene/manage depressive and stress symptoms.

The mechanism by which biophysical treatment exerts its anxiolytic effects is not yet understood. However, pre-clinical studies suggest that it may be linked to a range of modulatory factors such as anti-oxidants, growth factors and inflammatory mediators, although it is an area that remains controversial (12). Future studies are needed to characterise the mechanisms through which the biophysical effect derived from low electromagnetic waves exert these beneficial anxiolytic effects.

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