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ORIGINAL RESEARCH

Radioelectric brain stimulation in the treatment of generalized anxiety disorder with comorbid major depression in a psychiatric hospital: a pilot study

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Background: Generalized anxiety disorder (GAD) is often presented with major depression (MD). GAD-MD can be a chronic and disabling condition, and patients suffering from this disorder often respond poorly to psychopharmacological treatment and experience side effects with medication. Therefore, there is a high demand for effective nonpharmacological therapy for GAD-MD patients. The current study explores the use of a radioelectric asymmetric conveyer (REAC) device in the treatment of GAD-MD.

Methods: Participants were 24 patients diagnosed with GAD-MD being treated at a public psychiatric center. All patients were dissatisfied with their current pharmacological treatment. Patients were evaluated using the 21-item Hamilton Depression (HAM-D) rating scale and the Symptom Check List-90-Revised (SCL-90R) before and after REAC brain stimulation treatment cycles.

Results: After REAC brain stimulation treatment, all patients experienced a significant reduction in anxiety and depression. These results were confirmed by physician examination, HAM-D scores, and SCL-90R total scores.

Conclusion: These results indicate a role for REAC brain stimulation in the management of psychiatric conditions, specifically, GAD-MD comorbidity. REAC treatments are synergistic to drug therapy and appear to be helpful in reducing the side effects of medication. Future studies should evaluate the long-term effects of REAC treatment.

Keywords: anxiety disorders, depressive disorder, psychiatric somatic therapies, radioelectric asymmetric brain stimulation

Introduction

According to available epidemiological data, generalized anxiety disorder[1–4] (GAD) is the most common anxiety disorder[5–7] and one of the most common psychiatric conditions in the general population. The prevalence of GAD ranges from 4% to 8%. However, the actual figure for this condition is most likely double that number. Although GAD can be a chronic and disabling condition with a poor response to psychopharmacological treatment, it is one of the most unrecognized (both by the patient and the physician) and, consequently, undertreated mental pathologies.[1,8,9] Current therapies for GAD include serotonin and noradrenaline reuptake inhibitors[10–12] (eg, venlafaxine and duloxetine) and selective serotonin reuptake inhibitors[12–18] (eg, paroxetine and escitalopram), along with psychotherapeutic approaches,[19,20] such as cognitive behavioral therapy.[21–23] The delay in diagnosis, the chronic and continuous

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nature of the disorder, and importantly, inadequate response to current drug therapies may lead to demoralization, which often complicates GAD with major depression (MD). Unlike other psychiatric disorders, to date there are no known "physical" treatment options (eg, transcranial magnetic stimulation) for patients suffering from GAD comorbid with MD. While the majority of patients suffering from GAD-MD are treated by private psychiatrists,[24] the few who are seen in public psychiatric services are often seeking alternatives to traditional psychopharmacological treatment. The current study was conducted in a public psychiatry service outpatient setting with the goal of evaluating the efficacy of radioelectric asymmetric conveyer (REAC)[25,26] brain stimulation in patients with comorbid GAD and MD. REAC treatments have proven efficacy in ameliorating motor behavior abnormalities,[27] stress-related disorders, depression, anxiety,[28–33] and bipolar disorder.[34] In addition, REAC treatments are painless, noninvasive, and have no known adverse effects. The extensive use of "physical" approaches, such as REAC, as routine therapeutic protocols in the management of mental disorders, particularly those characterized by poor compliance and/or resistance to pharmacological treatment, is discussed.

Methods

The present study was approved by the Croce e Carle hospital ethics committee, Cuneo, Italy, and registered at the Australian New Zealand Clinical Trials Register. The study was conducted according to the principles of the Declaration of Helsinki.

Twenty-four outpatients (20 females and four males, mean age 46.7 ± 8.9 years) diagnosed with GAD-MD using current Diagnostic and Statistical Manual of Mental Disorders Fourth Revision criteria and the Symptom Checklist-90-Revised (SCL-90R)[35,36] participated in the study. The patients were being treated at the Psychiatric Hospital of Cuneo, Italy. All patients were dissatisfied with the results of their ongoing medical treatment of serotonin and noradrenaline reuptake inhibitors or selective serotonin reuptake inhibitors at a standard dose and duration of treatment. All participants were maintained on their current pharmacological treatment. At baseline (T0), the average 21-item Hamilton Depression (HAM-D)[37] rating scale score was 15.5 ± 4.6, corresponding to a "mild" level of severity. The SCL-90R and HAM-D were administered prior to and after a standard cycle of REAC treatments (one Neuro Postural Optimization[32] followed by 18 Neuro Psycho Physical Optimization[32] sessions). Nine SCL-90R clusters were examined, ie, somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychotic behavior. The SCL-90R was specifically used due to its greater sensitivity to critical clinical aspects of anxiety (ie, interpersonal sensitivity and phobic anxiety) than the classic Hamilton Anxiety Scale (HAM-A).[38] In addition, the overlap between HAM-D and HAM-A is well known.

REAC[25,26] was applied using a medical device based on an innovative biostimulation technology. REAC typically runs within a frequency range of 2.4, 5.8, or 10.5 gHz. For the current study, a frequency of 10.5 gHz, with a specific absorption rate of 7 μW/kg, was used. The REAC pulse protocol was seven radiofrequency bursts of 500 msec each, applied by touching the metallic tip of the REAC probe (Convogliatore di Radianza Modulante, Asmed, Italy) to the ear pavilion using Neuro Postural Optimization and Neuro Psycho Physical Optimization protocols which have been described in detail elsewhere.[31–34] The time interval from the initial clinical assessment until the last Neuro Psycho Physical Optimization session was approximately one month. Data were analyzed with *t*-tests, Wilcoxon signed-rank tests and Sign-tests. Statistical significance was set at $P < 0.05$.

Results

REAC treatments were well tolerated, with a good safety profile, and there were no withdrawals from the study due to side effects. After REAC treatment, all patients showed a significant reduction in anxiety and depression symptomatology. In addition, the clinical picture of each patient, as measured by physician evaluation, was described either as "improved" or "very improved." Moreover, clinical improvement was confirmed by psychometric test scores (Figures 1–4 and Table 1). The average HAM-D total score decreased from 15.5 ± 4.6 to 4.6 ± 2.2 ($t = 10.472$, $df = 46$, $P < 0.001$, see Figures 2 and 3). These results indicate an improvement from "mild depression" to an "absence of depression." Scores on all clusters of the SCL-90R scale were significantly decreased after REAC treatment. Table 1 and Figure 4 show results for each specific symptomatic cluster on the SCL-90R scale, providing a more accurate picture of the quality of the clinical response.

Discussion

REAC treatment resulted in significant decreases in both anxiety and depressive symptomatology. The remission of depressive symptomatology was demonstrated by a significant decrease in average HAM-D total score. All patients,

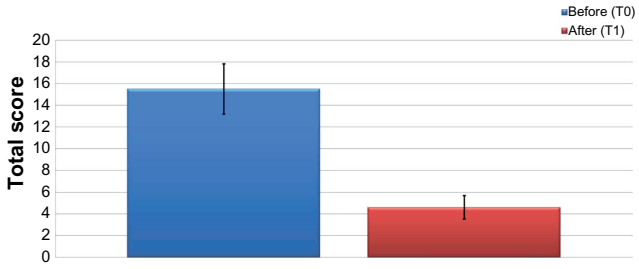

Figure 1 Hamilton Depression rating scale scores (means ± standard deviation).

after approximately 1 month of REAC treatment scored <8 on the HAM-D. In clinical terms, 1 month is similar to the delay of action of all categories of antidepressant and antianxiety medication.[39] In addition, there was a notable response of all SCL-90R clusters to REAC treatment. The remission of psychiatric symptomatology was maximally affected[27] in the majority of the clusters after Neuro Psycho Physical Optimization treatment. Moreover, the effect was observed in clusters that are typically refractory to the action of psychotropic drugs (ie, interpersonal sensitivity, somatization, and psychotic behavior). These results may be related to complex cortical dysregulation[40] which is not accessible to pharmacological action.

GAD-MD comorbidity often represents a psychopharmacological challenge, primarily due to a characteristic hypersensitivity to side effects coupled with the need for a high drug dosage. GAD-MD seems particularly sensitive to Neuro Psycho Physical Optimization treatments using REAC.[31–33] In addition, REAC treatment appears to protect patients from jitteriness syndrome,[41,42] which is frequently a cause of self-withdrawal from medication in GAD-MD patients.

REAC treatment appears to work synergistically with classic drug treatment, thereby optimizing clinical results.[34] Importantly, while all subjects continued medication during REAC treatment, many patients were able to reduce the dosage due to amelioration of their clinical condition. These results are particularly beneficial in patients who experience side effects from their medication.[34,30] Therefore, the reduction in drug dosage needed as a result of REAC treatment, significantly increased the safety and

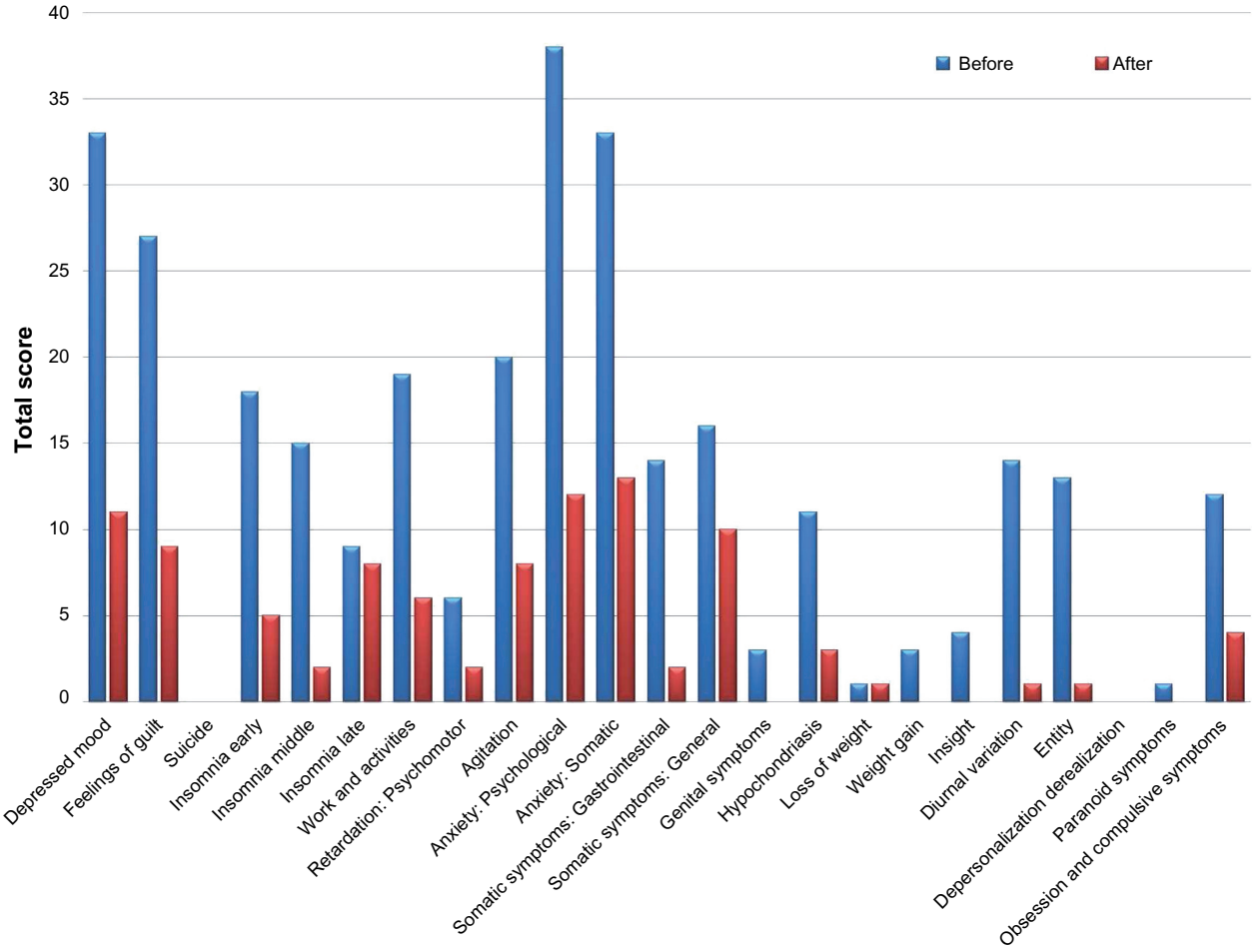

Figure 2 Hamilton Depression rating scale scores. Sum of the values of each cluster, before and after Neuro Psycho Physical Optimization treatment.

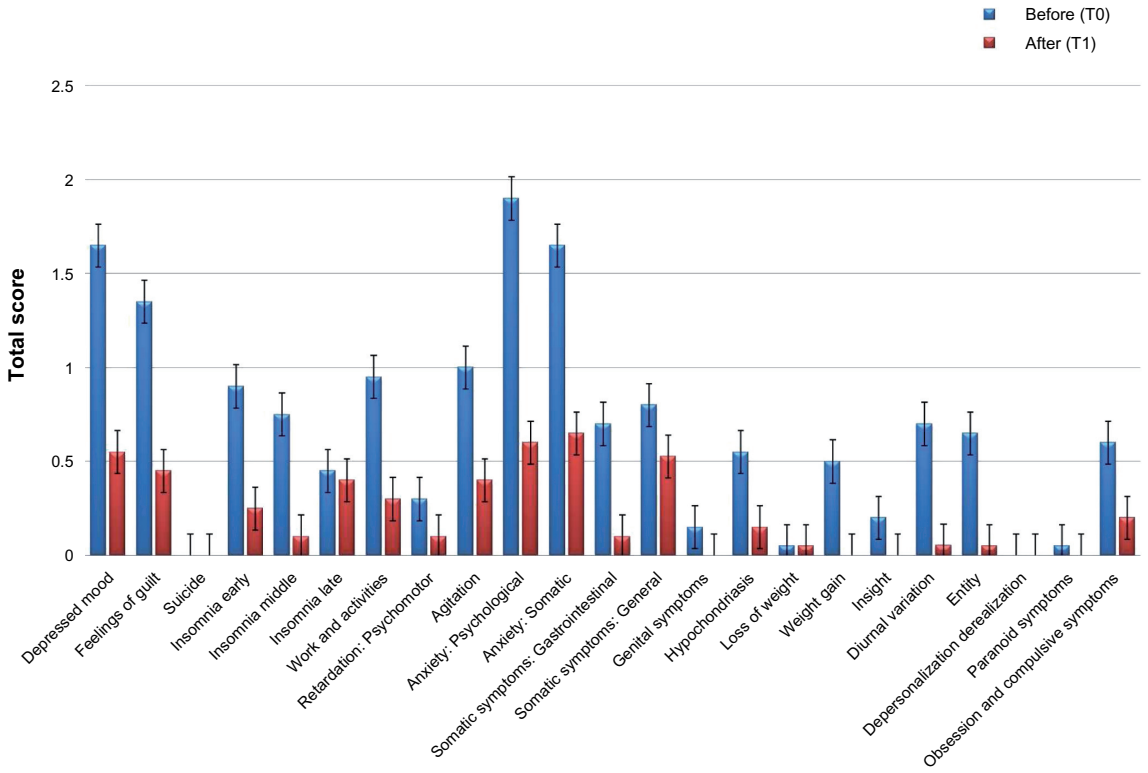

Figure 3 Hamilton Depression rating scale scores, mean of the value for each cluster, before and after Neuro Psycho Physical Optimization treatment.

tolerability profiles of serotonin and noradrenaline reuptake inhibitors and selective serotonin reuptake inhibitors.[43–49]

The mechanism of action of REAC treatment is mostly likely associated with remodulation of the abnormal brain activity seen in psychiatric disorders. This normalizing action appears to be crucial in anxiety disorders, where hyperfunctioning of newly developing, "reverberant," and short intracortical pathways is well established, and is most likely related to fear and avoidance behaviors.[50–52] Recent magnetic resonance imaging studies have confirmed these hypotheses.[34]

Subjects in the current study showed a good response to REAC. The marked and rapid clinical efficacy, along with

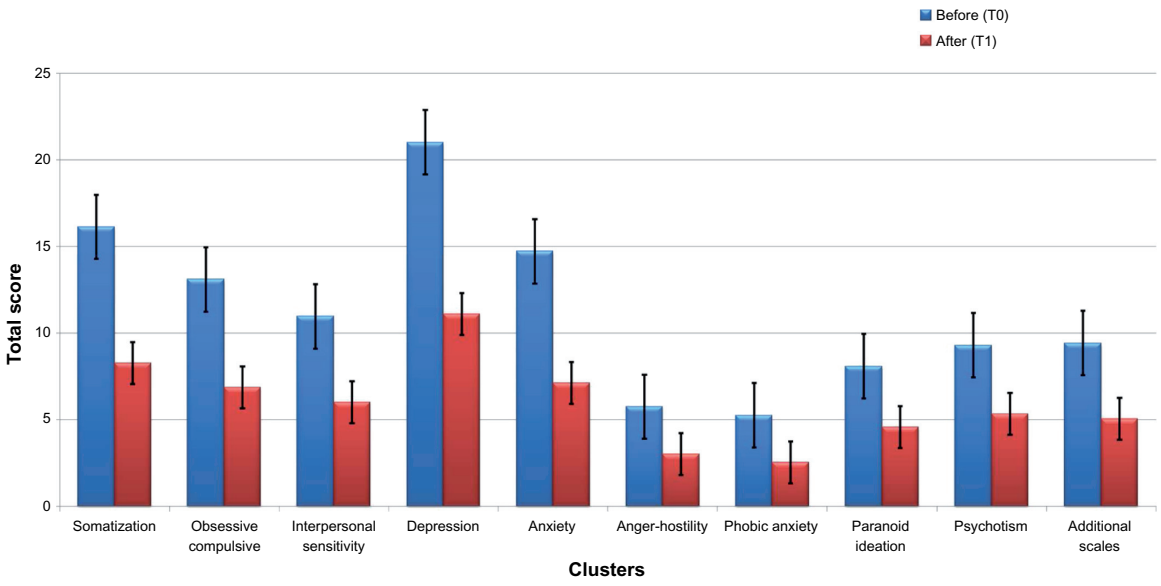

Figure 4 Mean value of each Symptom Check List-90-Revised cluster before and after Neuro Psycho Physical Optimization treatment.

Table 1 Symptom Check List-90-Revised statistics for each cluster

Statistics	Somatization	Obsession-compulsion	Interpersonal sensitivity	Depression	Anxiety	Anger hostility	Phobic anxiety	Paranoid ideation	Psychotic behavior
t-test	3.705	3.158	2.698	4.170	4.013	2.158	2.158	3.017	2.522
	DF 46	DF 46	DF 46	DF 46	DF 46	DF 46	DF 46	DF 46	DF 46
	$P = 0.000$	$P = 0.003$	$P = 0.010$	$P = 0.000$	$P = 0.000$	$P < 0.05$	$P < 0.05$	$P < 0.005$	$P < 0.05$
Wilcoxon	$Z = -3.639$	$Z = -4.016$	$Z = -3.795$	$Z = -3.776$	$Z = -4.293$	$Z = -3.605$	$Z = -2.989$	$Z = -3.895$	$Z = -3.240$
	0.000**	AS 0.000**	AS 0.000**	AS 0.000**	AS 0.000**	AS 0.000**	AS 0.003**	AS 0.000**	AS 0.001**
Sign test	ES 0.000**	ES 0.000**	ES 0.000**	ES 0.000***	ES 0.000***	ES 0.000***	ES 0.002***	ES 0.000***	ES 0.003***

Notes: **Asymp sig (two-tailed); ***Exact sig (two-tailed).
Abbreviations: AS, asymptotic significance (two-tailed); df, degree of freedom; ES, exact significance (two-tailed).

safety, tolerability, and ease of use, suggests more extensive use of REAC in public as well as private psychiatric settings, and the possibility of use in additional psychiatric disorders. The beneficial effects of REAC treatment in bipolar disorder have recently been demonstrated.[34]

Amelioration of psychiatric symptoms using typical pharmacological treatments is elusive, and therefore, an innovative medical device such as REAC may serve as a beneficial adjunct. Moreover, REAC treatment sessions allow the physician to establish a close and more continuous relationship with patients. The doctor-patient relationship has been shown to be critical in promoting adherence to prescribed therapies.

While the current study was conducted exclusively in ambulatory patients, the advantages of REAC treatment may prove to be beneficial in the treatment of hospitalized patients. Further studies in a greater number of patients, using double-blind and placebo-controlled protocols, are needed. Long-term studies designed to evaluate the stability of REAC treatment are also required.

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Disclosure

Salvatore Rinaldi and Vania Fontani are the inventors of the radioelectric asymmetric conveyer system.

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