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 disorder¹⁻⁴ (GAD) is the most common anxiety disorder⁵⁻⁷ 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 inhibitors¹⁰⁻¹² (eg, venlafaxine and duloxetine) and selective serotonin reuptake inhibitors¹²⁻¹⁸ (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 Optimization³² followed by 18 Neuro Psycho Physical Optimization³² 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 $7 \mu\text{W/kg}$, 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 $\pm$ 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 anti-anxiety medication.³⁹ In addition, there was a notable response of all SCL-90R clusters to REAC treatment. The remission of psychiatric symptomatology was maximally affected²⁷ 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 dysregulation⁴⁰ 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 DF 46 P = 0.000	3.158 DF 46 P = 0.003	2.698 DF 46 P = 0.010	4.170 DF 46 P = 0.000	4.013 DF 46 P = 0.000	2.158 DF 46 P < 0.05	2.158 DF 46 P < 0.05	3.017 DF 46 P < 0.005	2.522 DF 46 P < 0.05
Wilcoxon	Z = -3.639 0.000**	Z = -4.016 AS 0.000**	Z = -3.795 AS 0.000**	Z = -3.776 AS 0.000**	Z = -4.293 AS 0.000**	Z = -3.605 AS 0.000**	Z = -2.989 AS 0.003**	Z = -3.895 AS 0.000**	Z = -3.240 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.

References

- Baldwin DS, Ajel KI, Garner M. Pharmacological treatment of generalized anxiety disorder. *Curr Top Behav Neurosci*. 2010;2: 453–467.
- Mackenzie CS, Reynolds K, Chou KL, Pagura J, Sareen J. Prevalence and correlates of generalized anxiety disorder in a national sample of older adults. *Am J Geriatr Psychiatry*. 2011;19:305–315.
- Michelson SE, Lee JK, Orsillo SM, Roemer L. The role of values – consistent behavior in generalized anxiety disorder. *Depress Anxiety*. 2011;28:358–366.
- Newman MG, Llera SJ. A novel theory of experiential avoidance in generalized anxiety disorder: a review and synthesis of research supporting a contrast avoidance model of worry. *Clin Psychol Rev*. 2011;31: 371–382.
- Bruce TJ, Saeed SA. Social anxiety disorder: a common, underrecognized mental disorder. *Am Fam Physician*. 1999;60:2311–20.
- el-Miedany YM, el-Rasheed AH. Is anxiety a more common disorder than depression in rheumatoid arthritis? *Joint Bone Spine*. 2002;69: 300–306.
- Zamorski MA, Ward RK. Social anxiety disorder: common, disabling, and treatable. *J Am Board Fam Pract*. 2000;13:251–260.
- Goncalves DC, Pachana NA, Byrne GJ. Prevalence and correlates of generalized anxiety disorder among older adults in the Australian National Survey of Mental Health and Well-Being. *J Affect Disord*. 2011;132:223–230.

9. Blondeau J, Bouvette A. Generalized anxiety disorder: recognizing it and understanding its impact on the cognitive functioning. *Sante Ment Que.* 2010;35:221–245. French.
10. Cravello L, Caltagirone C, Spalletta G. The SNRI venlafaxine improves emotional unawareness in patients with post-stroke depression. *Hum Psychopharmacol.* 2009;24:331–336.
11. Sclar DA, Robison LM, Skaer TL. Concomitant triptan and SSRI or SNRI use: a risk for serotonin syndrome. *Headache.* 2008;48:126–129.
12. Vlahiotis A, Devine ST, Eichholz J, Kautzner A. Discontinuation rates and health care costs in adult patients starting generic versus brand SSRI or SNRI antidepressants in commercial health plans. *J Manag Care Pharm.* 2011;17:123–132.
13. Bitran S, Farabaugh AH, Ameral VE, et al. Do early changes in the HAM-D-17 anxiety/somatization factor items affect the treatment outcome among depressed outpatients? Comparison of two controlled trials of St John's wort (*Hypericum perforatum*) versus a SSRI. *Int Clin Psychopharmacol.* 2011;26:206–212.
14. Haliburn J. Adolescent suicide and SSRI antidepressants. *Australas Psychiatry.* 2010;18:587.
15. McCabe C, Mishor Z, Filippini N, Cowen PJ, Taylor MJ, Harmer CJ. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. *Mol Psychiatry.* 2011;16:592–594.
16. Rucci P, Frank E, Scocco P, et al. Treatment-emergent suicidal ideation during 4 months of acute management of unipolar major depression with SSRI pharmacotherapy or interpersonal psychotherapy in a randomized clinical trial. *Depress Anxiety.* 2011;28:303–309.
17. Sansone RA, Sansone LA. SSRI-induced indifference. *Psychiatry (Edgmont).* 2010;7:14–18.
18. Silver H, Susser E, Danovich L, et al. SSRI augmentation of antipsychotic alters expression of GABA(A) receptor and related genes in PMC of schizophrenia patients. *Int J Neuropsychopharmacol.* 2011;14:573–584.
19. Gosselin P, Ladouceur R, Morin CM, Dugas MJ, Baillargeon L. Benzodiazepine discontinuation among adults with GAD: a randomized trial of cognitive-behavioral therapy. *J Consult Clin Psychol.* 2006;74:908–919.
20. Ladouceur R, Leger E, Dugas M, Freeston MH. Cognitive-behavioral treatment of generalized anxiety disorder (GAD) for older adults. *Int Psychogeriatr.* 2004;16:195–207.
21. Gaudiano BA. Review: cognitive behavioural therapy is an effective treatment for depression, panic disorder, and generalised anxiety disorder, but may be less effective in severe cases. *Evid Based Ment Health.* 2006;9:80.
22. Haby MM, Donnelly M, Corry J, Vos T. Cognitive behavioural therapy for depression, panic disorder and generalized anxiety disorder: a meta-regression of factors that may predict outcome. *Aust N Z J Psychiatry.* 2006;40:9–19.
23. Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry.* 2004;185:46–54.
24. Davidson JR, Feltner DE, Dugar A. Management of generalized anxiety disorder in primary care: identifying the challenges and unmet needs. *Prim Care Companion J Clin Psychiatry.* 2010;12(2).
25. Rinaldi S, Fontani V, inventors; Rinaldi S, Fontani V, assignees. Radioelectric asymmetric conveyer for therapeutic use. US patent EP1301241 (B1). October 11, 2006.
26. Rinaldi S, Fontani V, inventors; Rinaldi S, Fontani V, assignees. Radioelectric asymmetric conveyer for therapeutic use. US patent 7,333,8592001.
27. Castagna A, Rinaldi S, Fontani V, Mannu P. Radioelectric asymmetric brain stimulation and lingual apex repositioning in patients with atypical deglutition. 2011;4:209–213.
28. Castagna A, Rinaldi S, Fontani V, Aravagli L, Mannu P, Margotti ML. Does osteoarthritis of the knee also have a psychogenic component? Psycho-emotional treatment with a radio-electric device vs intra-articular injection of sodium hyaluronate: an open-label, naturalistic study. *Acupunct Electrother Res.* 2010;35:1–16.
29. Collodel G, Moretti E, Fontani V, et al. Effect of emotional stress on sperm quality. *Indian J Med Res.* 2008;128:254–261.
30. Mannu P, Rinaldi S, Fontani V, Castagna A, Lotti Margotti M. Radio electric treatment vs es-citalopram in the treatment of panic disorders associated with major depression: an open-label, naturalistic study. *Acupunct Electrother Res.* 2009;34:135–149.
31. Rinaldi S, Fontani V, Aravagli L, Margotti ML. Psychological and symptomatic stress-related disorders with radio-electric treatment: psychometric evaluation. *Stress and Health.* 2010;26(5):350–358.
32. Rinaldi S, Fontani V, Aravagli L, Mannu P. Psychometric evaluation of a radio electric auricular treatment for stress related disorders: a double-blinded, placebo-controlled controlled pilot study. *Health Qual Life Outcomes.* 2010;8:31.
33. Rinaldi S, Fontani V, Moretti E, et al. A new approach on stress-related depression and anxiety: neuro-psycho-physical-optimization with radio electric asymmetric conveyer. *Indian J Med Res.* 2010;132:189–194.
34. Mannu P, Rinaldi S, Fontani V, Castagna A. Long-term treatment of bipolar disorder with a radioelectric asymmetric conveyer. *Neuropsychiatr Dis Treat.* 2011;7:373–379.
35. Pedersen G, Karterud S. Is SCL-90R helpful for the clinician in assessing DSM-IV symptom disorders? *Acta Psychiatr Scand.* 2004;110:215–224.
36. Olsen LR, Mortensen EL, Bech P. The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. *Acta Psychiatr Scand.* 2004;110:225–229.
37. Serrano-Duenas M, Soledad Serrano M. Concurrent validation of the 21-item and 6-item Hamilton Depression Rating Scale versus the DSM-IV diagnostic criteria to assess depression in patients with Parkinson's disease: an exploratory analysis. *Parkinsonism Relat Disord.* 2008;14:233–238.
38. Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. *BMC Psychiatry.* 2007;7:7.
39. Tadic A, Wagner S, Gorbulev S, et al. Peripheral blood and neuropsychological markers for the onset of action of antidepressant drugs in patients with major depressive disorder. *BMC Psychiatry.* 2011;11:16.
40. Carver CS, Johnson SL, Joormann J. Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: what depression has in common with impulsive aggression. *Psychol Bull.* 2008;134:912–943.
41. Bennett JA, Moioffer M, Stanton SP, Dwight M, Keck PE Jr. A risk-benefit assessment of pharmacological treatments for panic disorder. *Drug Saf.* 1998;18:419–430.
42. Sinclair LI, Christmas DM, Hood SD, et al. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. *Br J Psychiatry.* 2009;194:483–490.
43. Byrd L. Serotonin syndrome: what is it? causes, recognition, and management. *Geriatr Nurs.* 2010;31:387–389.
44. Coster S, Visser MH, Touw DJ, Wirtz PW. Serotonin syndrome with sertraline and indomethacin. *J Clin Psychopharmacol.* 2010;30:468–470.
45. Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache.* 2010;50:1089–1099.
46. Lawyer TI, Jensen J, Welton RS. Serotonin syndrome in the deployed setting. *Mil Med.* 2010;175:950–952.
47. Peacock LE, Wright F. Serotonin syndrome secondary to tramadol and citalopram. *Age Ageing.* 2011;40:528.
48. Rothrock JF. Triptans, SSRIs/SNRIs and serotonin syndrome. *Headache.* 2010;50:1101–1102.
49. Sanyal D, Chakraborty S, Bhattacharyya R. An interesting case of serotonin syndrome precipitated by escitalopram. *Indian J Pharmacol.* 2010;42:418–419.

50. Rockstroh BS, Wienbruch C, Ray WJ, Elbert T. Abnormal oscillatory brain dynamics in schizophrenia: a sign of deviant communication in neural network? *BMC Psychiatry*. 2007;7:44.
51. Rissling AJ, Makeig S, Braff DL, Light GA. Neurophysiologic markers of abnormal brain activity in schizophrenia. *Curr Psychiatry Rep*. 2010; 12:572–578.
52. Kirby ED, Friedman AR, Covarrubias D, et al. Basolateral amygdala regulation of adult hippocampal neurogenesis and fear-related activation of newborn neurons. *Mol Psychiatry*. June 14, 2011. [Epub ahead of print.]

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