Scientific Research Publishing

Open Journal of Psychiatry, 2019, 9, 138-152
http://www.scirp.org/journal/ojpsych
ISSN Online: 2161-7333
ISSN Print: 2161-7325

Semantic and Phonemic Verbal Fluency Performance in Patients with General Anxiety Disorders and Allostatic Load under Alprazolam Treatment

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How to cite this paper: Soria, C.A., Remedi, C., D'Alessio, L. and Roldán, E.J.A. (2019) Semantic and Phonemic Verbal Fluency Performance in Patients with General Anxiety Disorders and Allostatic Load under Alprazolam Treatment. *Open Journal of Psychiatry*, **9**, 138-152.
https://doi.org/10.4236/ojpsych.2019.92011

Received: February 22, 2019
Accepted: March 23, 2019
Published: March 26, 2019

Abstract

Purpose: Anxiety disorders are frequently associated with chronic stress with possible cognitive consequences. The aim of this study was to determine the verbal fluency performance in a cohort of patients with anxiety disorders and allostatic load, treated with alprazolam during 12 weeks. **Methods:** Patients with GAD (general anxiety disorders, DSM IV), with >6 in Hamilton Anxiety Rating Scale (HAM-A), neuroticism > 18 (NEO-FFI inventory), and normal Mini-Mental State Examination were included. Clinical and Psychiatric examination, Allostatic Load Index and cognitive assessment were analyzed before and after 12 weeks of treatment. The phonemic and semantic verbal fluency tests were determined in all patients. The scoring for each fluency task was determined by counting the number of correct words. The total score from each semantic and phonemic verbal task was analyzed comparing the individual score with normal data controlled by age and sex. Patients with scores > −2 standard deviation (SD) from normative data were considered impaired. **Results:** Fifty-four patients completed the semantic verbal fluency test before treatment and fifty patients completed after treatment. According to the z-scores before treatment 7 patients of 54 (12.9%) had verbal fluency impairments. After treatment none patients showed semantic verbal fluency deficits but 3 patients of 50 (6%) showed phonemic impairments. Impaired group was significantly associated with an older age before treatment ($p = 0.033$) and with a similar tendency but not significant ($p = 0.09$) after treatment (Student t test). **Conclusion:** In this study older age factor was associated with verbal fluency impairment in GAD patients. Stratified treatments

analyzing age and sex factors, including allostatic load measurements and cognitive assessments may be useful tools to determine the effectiveness and the safety of psychopharmacological treatments.

Keywords

Verbal Fluency Test, Chronic Stress, Allostatic Load, Sex, Age

1. Introduction

Stressors trigger physiological and behavioural responses that are aimed at reinstating homeostasis. If the stress response is inadequate or excessive and prolonged (chronic stress), the cost of reinstating homeostasis might become too high and predisposed individuals at an increased risk of (mental) illness such as general anxiety disorder [1] [2]. Chronic stress has been demonstrated to induce functionally-relevant effects on hippocampus and prefrontal cortex brain neuroplasticity due to hypothalamic-pituitary-adrenal axis (HPA)[1] hyperactivity, traduced on impairments in cognition [3]-[8].

Verbal and non-verbal fluency performance have been previously studied in patients with attention deficit hyperactivity disorder [9] and in patients with obsessive compulsive disorder [10] and also in subjects with stress related conditions such as neuroticism [11], showing lower scores and impairments among these patients. In this line, other authors have been proposed that anxiety may modify neural activation during the performance of verbal fluency tasks, executive functions that are dependent on the frontal lobe function [12].

On the other side, the use of drugs such as benzodiazepines is effective in promptly reducing anxiety scores but may have controversial effects on cognition after long term use [13]-[18]. Nevertheless, there are not conclusive findings regarding verbal fluency, an executive function which depends on frontal lobe functions, in patients with general anxiety disorders treated with benzodiazepines [18] [19].

The rate of the outpatients' use of benzodiazepines has been increased substantially in the last years, especially among clinicians, psychiatrists and neurologists [20]; indeed clinical studies are continually needed to determine safety in long term uses. The GEMA project (Gador Study of Stress Modulation by Alprazolam) [21] consists of a series of consecutive studies performed on a group of high symptomatic outpatients with general anxiety disorder (GAD)[2] associated with chronic stress, determined by high allostatic load (AL) levels (indicators for the functioning of the main potentially stress affected systems) [22] [23] and neuroticism (a clinical condition well-known as a stress vulnerability factor and defined as an exaggerated response to psychosocial stressors with intense emotional reaction) [24] [25] [26] [27].

[1](HPA) Hypothalamic-pituitary-adrenal axis.
[2](GAD) General Anxiety Disorder

In a previous analysis performed by our group in the same cohort of patients, we analyzed the AL index and determined the effects of sex and age on allostatic load variables before and after treatment [28]. In this study we found that female sex was associated with higher levels of anxiety with a better profile in the same allostatic load variables such as cardiovascular ones. Hereby, in the present report we aimed to determine the verbal fluency performance at basal conditions (before treatment) and after 12 weeks of treatment with alprazolam (a positive allosteric modulator of GABA A receptor), including sex and age as influential factors.

2. Methods

In this prospective study patients were recruited during 3 years up to 2014. The database is currently locked and subjected to multiple analyses. Inclusion criteria were Hamilton Anxiety Rating Scale (HAM-A)[3] [29] > 6, a minimum score of 18 points in the NEO-FFI neuroticism scale [30] and at least one positive criterion for AL load index modified from Seeman and Crimmins 2003 [22] (clinical manifestations were under personalized medical treatment and were stable). All patients had a normal performance in the Mini-Mental State Examination [31] with general good vision and hearing with or without the use of aids. Exclusion criteria were: subjects with depression and/or other comorbid diseases listed under axis I of the DSM-IV, (American Psychiatric Association, 1994), patients taking psychotropic drugs, sympathomimetic, corticosteroid and/or any other medication that might interact with alprazolam; persons who were hypersensitive to drugs; with confirmed or suspected gestation; women likely to become pregnant during the study; patients with an important clinical condition that required treatment modification and that might interfere with the study treatment or evaluation methods.

The protocol was evaluated in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) and Argentine clinical practice guideline, by the Independent Ethics Committee of Foundation for Pharmacological Studies and Drugs, Buenos Aires and then submitted to the national regulatory authority (ANMAT, Disposition #61409-8) and to the provincial regulatory authority, under the responsibility of the Ministry of Health of Córdoba Province (Dossier #1296). The trial is also registered at WHO (Word Health Organization)[4] trial registration data set. Results were reported to the Argentine regulatory agency ANMAT in accordance with regulations in force. All patients signed the informed consent form.

2.1. Clinical Assessment

In this trial all determinations were analyzed periodically (see Soria *et al.* 2005 for details) [21]. In the present study, we report the changes in verbal fluency

[3](HAM-A) Hamilton Anxiety Rating Scale.
[4](WHO) World Health Organization.

tests and the correlations with clinical variables, after 12 weeks of treatment with reference to the basal status.

Anxiety assessment: All patients included in this study met criteria for general anxiety disorder codified in Axis I of DSM IV (American Psychiatric Association) [32], and psychiatric assessment was determined by experimented clinical psychiatrists. In all patients the HAM-A [29] of 14 items was determined, (>6 points indicated anxiety and ≥15 points indicated moderate to severe anxiety).

Allostatic Load assessment: For measuring AL index, 18 clinical and laboratory parameters were determined during the morning (10 ± 1 hour AM). One point was added for each abnormal parameter up or under the cut off points according to Crimmins and Seeman criteria modified (2) [1]: 1—Systolic blood pressure > 140 mmHg and/or; 2—diastolic pressure >90 mmHg; 3—BMI2 (body mass index) > 25; 4—waist-hip ratio (indexes of adipose tissue deposition) more than >1 in men and >0.8 in women; 5—total cholesterol > 200 mg/dl; 6—LDL (low density lipoprotein) > 120 mg/dl; 7—HDL (high density lipoprotein) > 37 mg/dl; 8—total cholesterol/HDL ratio > 3.5 mg/dl; 9—triglycerides > 200 mg/dl; 10—creatinine > 1.2 mg/dl; 11—albumin < 3.5 g/dl; 12—C-reactive protein (CRP) > 7.1 mg/L; 13—fibrinogen > 400 mg/dl; 14—glycated hemoglobin > 6 mg/dl; 15—salivary cortisol > 32 nM; 16—salivary methoxy-hydroxy-phenylglycol (MHPG) (noradrenaline metabolite) > 2750 nM; 17—serum dehydro-epi-androsterone (DHEA) < 80 ng/ml in men and <35 ng/ml in women; 18—serum noradrenaline levels > 100 pg/ml.

Cognitive assessment: The phonemic and semantic verbal fluency tests were determined in all patients [33]. On the semantic verbal fluency task participants had to name as many animals as possible within two minutes. Words that were not identifiable as animals were considered rule violations and the examiner recorded all correct words. On the phonemic verbal fluency task the patients were asked to name within 2 minutes, as many different words as possible beginning with the letter p. Words beginning with another letter and/or perseverations were considered rule violations. The scoring for each fluency task was determined by counting the number off correct words excluding the number of rule violations and repetitions. The tests were applied after 6 hours since the last administration of alprazolam (nadir plasma). Cognitive tests were blinded to the evaluator. In this report we analyzed the scores at two moments, before and after treatment. The total score from each semantic and phonemic verbal tasks were analyzed comparing the individual score with normal data controlled by age and sex. Patients with scores > −2 standard deviation (SD) from normative data controlled by age and sex were considered impaired [33].

2.2. Treatment Instauration

Patients admitted into the study were given alprazolam tablets (Alplax®, Gador SA, Buenos Aires; batch number 03730), in a flexible dosing regimen within 0.25

to 1 mg t.i.d. (three times a day), which enabled a dose-response analysis for the variables under investigation. Individual doses were determined according to clinical criteria by the researcher responsible for each patient, and the lowest effective dose was administered in each case. The alprazolam's dosage schedule was maintained for 12 weeks. Subsequently, the investigator decided to continue or discontinue treatment. All participants have been warned about alprazolam's depressant effects and the possible risks in activities that required alert. Alcohol consumption during the observational period was not recommended. Patients were also monitored to detect risk of suicide and/or overdose. All adverse events were monitored according to good clinical practice standards of the local regulatory authority; National Administration of Drugs, Foods and Medical Devices (ANMAT) and the Ministry of Health, Province of Córdoba.

2.3. Statistics

Descriptive statistics of quantitative variables were determined and compared. The sample size was calculated considering changes in variables higher than 25% with a 1-β power of 0 - 80 to be detected. Statistical significance was considered at $p < 0.05$ (2-sided; 1-β power ≥ 0.80). To analyze sex and age factors ($\geq$ or <50 years old) effects on total scores of cognitive parameters, a general univariate lineal model (Two-way ANOVA) was applied for each AL variable measured before and after treatment. Interactions between factors were also analyzed, and the effect size was calculated using the partial eta squared (hp^2). Effect size > 0.09 was considered strong, between 0.02 and 0.09 is moderate and ≤0.02 is statistically significant but weak. Student t test was determined to compare impaired versus no-impaired group. Spearman (non-parametric) and/or Pearson (parametric) tests were used to determine the correlation coefficient: $r \geq 0.80$ and $p < 0.05$ (2-sided) was considered as strong correlation, $r = 0.50 < r < 0.80$ and $p < 0.05$ (2-sided), was considered a moderate correlation and $r \geq 0.3$ and <0.5 and $p < 0.05$ (2-sided) was considered a low correlation [34].

3. Results

In this analysis, fifty-four patients completed the semantic verbal fluency test (35 women and 19 men), and 53 (35 women and 18 men) the phonemic verbal fluency test at basal. According age, at basal 26 patients had ≥50 years old, and 28 patients < 50 years. After treatment fifty patients completed both semantic and phonemic verbal fluency tests. Changes in the individual allostatic variables in this sample and psychiatric variables were described in detail in a previous publication [28]. The VFT scores according age a sex are resumed in **Table 1** and **Table 2**. No differences were found regarding sex and age factors in this sample analyzing the total score (Two way ANOVA) either at basal or at week 12. In a second analysis, the z-scores corrected by age and sex for each patient, were determined before and after treatment. Before treatment 7 patients of 54 (12.9%) had verbal fluency impairments (z-score > −2 comparing with normative data

Table 1. Sex differences in cognitive performance before and after treatment.

Clinical and Cognitive Assessments (Scores)	Sex	n	X	SD	Two-way ANOVA = p value	Partial eta squared (hp^2)
Hamilton Anxiety Scale (HAM-A)						
Basal	Females	35	31.7	10.2	3.7 (1,50) = 0.05	0.069
	Males	19	28.2	6.4		
w12	Females	31	14.4	5.7	8.82 (1,46) = 0.005*	0.161
	Males	19	9.4	5.8		
Total Allostatic Index						
Basal	Females	35	5.4	2.3	1.08 (1,50) = 0.30	0.021
	Males	19	6.0	2.2		
w12	Females	31	4.6	2.5	2.13 (1,46) = 0.15	0.044
	Males	19	5.4	1.9		
Verbal Fluency Test (Semantic)						
Basal	Females	35	20.0	5.2	0.006 (1,50) = 0.94	0.001
	Males	19	20.0	4.8		
w12	Females	31	23.5	5.0	0.45 (1,46) = 0.23	0.03
	Males	19	25.3	6.3		
Verbal Fluency Test (Phonemic)						
Basal	Females	35	12.9	3.9	0.27 (1,49) = 0.6	0.006
	Males	18	12.1	4.8		
w12	Females	31	14.52	4.1	0.25 (1,46) = 0.6	0.021
	Males	19	13.74	3.5		

W12: Week 12, n (number of patients), X = mean, SD = standard deviation. hp^2 = Effect size. *$p < 0.05$.

matched by age and sex); 5 patients showed impairments in semantic verbal fluency, 2 patients in phonemic verbal fluency and 1 showed both semantic and phonemic impairments. After treatment none patients showed semantic verbal fluency deficits but 3 patients of 50 (6%) showed phonemic impairments (Figure 1).

In an ulterior analysis we compared the clinical variables (psychiatric, allostatic load and pharmacological variables), between impaired and no-impaired subjects before and after treatment. Impaired group was significantly associated to older age before treatment ($p = 0.033$) with a tendency but not significant ($p = 0.09$) after treatment (Student t test) (Figure 2). Pearson correlations between allostatic load individual parameters and verbal fluency tasks (z scores), showed a low correlation between phonemic verbal fluency and noradrenaline levels after treatment ($r = 0.31$, $p = 0.03$). Also a tendency to a negative correlation

Table 2. Age differences in cognitive performance before and after treatment.

Clinical and Cognitive Assessments (Scores)	Age (Years = ys)	n	χ	SD	Two-way ANOVA F (df) = p value	Partial eta squared (hp^2)
Hamilton Anxiety Scale (HAM-A)						
Basal	≥50 ys	26	31.4	8.1	0.01 (1,50) = 0.97	0.001
	<50 ys	28	30.9	8.3		
w12	≥50 ys	24	13.1	6.4	0.03 (1,46) = 0.90	0.000
	<50 ys	26	11.9	6.1		
Total Allostatic Load Index						
Basal	≥50 ys	26	6.1	1.8	3.31 (1,50) = 0.07	0.062
	<50 ys	28	5.1	2.4		
w12	≥50 ys	24	5.7	2.1	5.98 (1,46) = 0.02*	0.115
	<50 ys	26	4.1	2.3		
Verbal Fluency Test (Semantic)						
Basal	≥50 ys	26	19.7	5.9	0.01(1,50) = 0.89	0.001
	<50 ys	28	20.3	4.1		
w12	≥50 ys	24	24.4	5.8	0.27(1,46) = 0.63	0.006
	<50 ys	26	24.0	5.3		
Verbal Fluency Test (Phonemic)						
Basal	≥50 ys	26	12.1	4.1	0.76(1,49) = 0.80	0.015
	<50 ys	27	13.1	4.4		
w12	≥50 ys	24	14.5	4.3	0.69(1,46) = 0.40	0.015
	<50 ys	26	13.9	3.5		

W12: Week 12, n (number of patients), X = mean, SD = standard deviation. hp^2 = Effect size. *p < 0.05.

was found between DHEA plasmatic levels (r = −027, p = 0.04) and phonemic verbal fluency z-score at basal (Figure 3). Additionally, Pearson correlations between verbal fluency tests, showed an inverse correlation tendency between neuroticism score and phonemic verbal fluency score at basal (r = −0.258, p = 0.068).

4. Discussion

In this study we included a special sample of very symptomatic patients with GAD associated to AL (a clinical index of chronic stress) and neuroticism (a psychological condition associated to an exaggerated response to psychosocial stressors). These patients underwent long-term treatment (12 weeks) with alprazolam in low doses (1.5 to 3 mg/day). The high-potency BZD alprazolam (a triazolo-benzodiazepine), produces a positive allosteric modulation of $GABA_A$

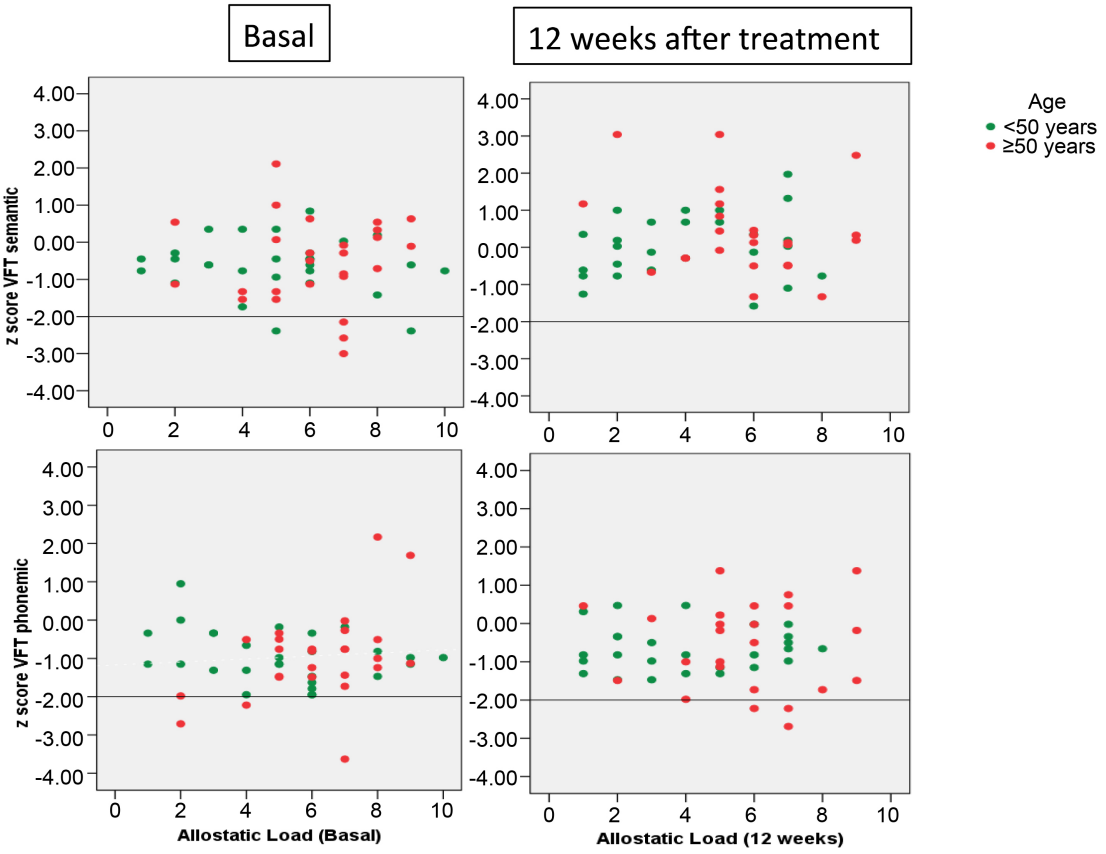

Figure 1. Verbal Fluency Test (VFT), semantic and phonemic z-scores in function of the allostatic load index in patients with general anxiety disorder treated during 12 weeks with alprazolam.

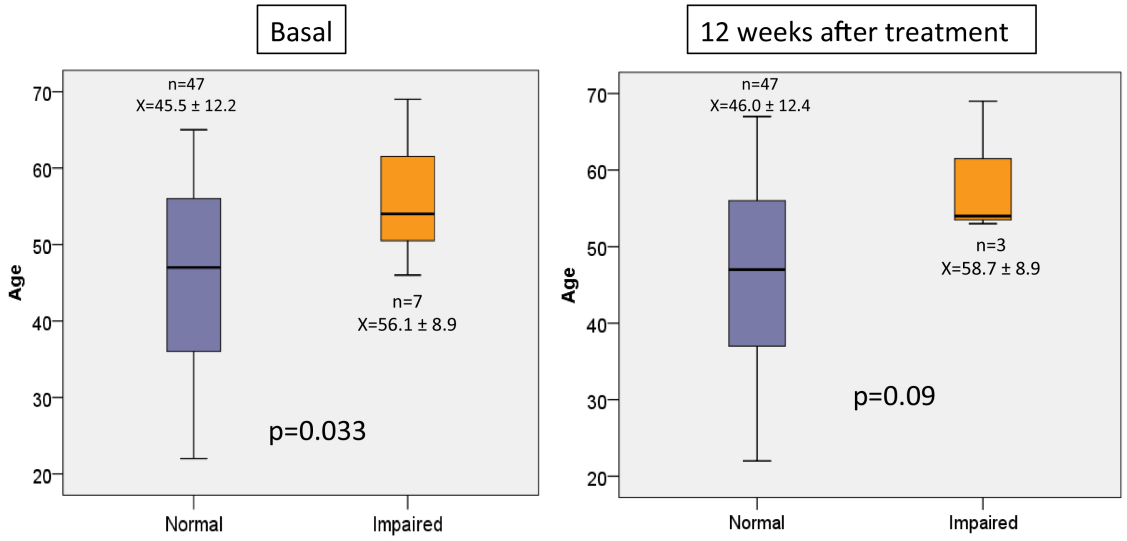

Figure 2. Age comparison of subjects with general anxiety disorder and allostatic load treated during 12 weeks with alprazolam according to the performance in the VFT (z-scores). Blue boxes represent patients with normal VFT (z-scores ≤ −2 SD), and orange boxes represent patients with impaired VFT (z-scores > −2 SD).

receptor. Alprazolam administered in relatively low doses may has a positive effect on individuals with anxiety disorders associated with chronic stress, and has

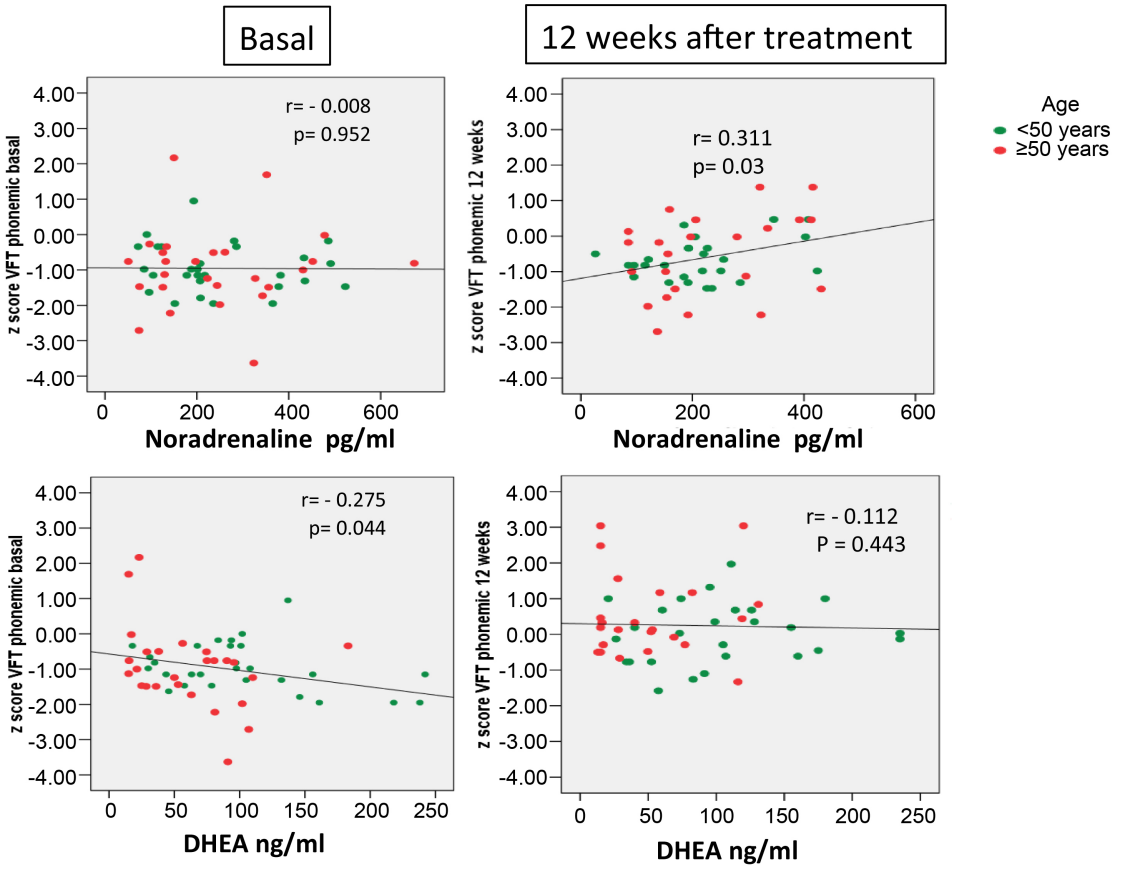

Figure 3. Pearson correlations between cognitive variables (Phonemic VFT) and allostatic load variables. Phonemic VFT inversely correlated with DHEA plasmatic levels at basal and positively correlated with noradrenaline plasmatic levels at 12 weeks.

been proposed to have less impact on cognitive functions because of the shorter acting and the lower doses required [18] [21]. Nevertheless, the risk of inducing pharmacological dependence and/or cognitive adverse events have been described, indeed it should be regarded with caution [13] [14] [15] [16] [17] [35] [36] [37]. In the present report, older age was the main factor involved in the verbal fluency alterations observed before and after alprazolam treatment. Before treatment a 13% was found impaired. After treatment, phonemic but not semantic verbal fluency was found impaired in a few cases. Older age is a known factor involved in cognition impairment, and has been proposed as a warning factor for developing cognitive decline induced by drugs, particularly benzodiazepines [18] [36] [38]-[43]. Additionally, in this study, the noradrenaline levels showed a low correlation with verbal fluency scores after treatment, suggesting that noradrenergic function may be a potential regulator of these functions with a potential dual effect (deleterious effect in high levels but also in very low levels). Similar to this results, other researchers determined lower salivary levels of MHPG in anxious patients treated with alprazolam [24] [44] [45] and in normal subjects who received the drug [46]. Similarly to these authors, we described in a previous report the reduction of MHPG (the main noradrenaline metabolite) and

noradrenaline, 12 weeks after treatment with alprazolam, contributing to reduce AL [28]. In this regard an increment of noradrenergic function was described in patients with anxiety disorders [47] [48]. Indeed, periodic dosages of allostatic load biochemical parameters may be an easy method to complete the clinical analysis during the follow up of treated patients.

Chronic stress has demonstrated to induce negative effects on cognitive functions and on emotional regulation, altering neuroendocrine and autonomic functions [8]. Chronic stress may impairs cognitive function [49] and has negative effects on cerebral neuroplasticity affecting dendritic arbor and synapses number in specific brain regions, including the hippocampus, amygdala and the prefrontal cortex. Chronic elevated levels of glucocorticoids may reduce memory processes (declarative memory) by affecting the normal hippocampal neuroplasticity and functionality [49] [50] [51]. Furthermore, stress-related events upon the prefrontal cortex may have deleterious actions in working memory (the short term memory that keep events in mind) which is also an executive function depending on frontal lobe normal functioning [52]. Not only chronic stress affects cognition, also anxiety by itself can modify executive functions. It has been proposed that anxiety as a personality trait reduces executive cognitive functions by impairing attention and task-switching capacity [53]. Gwada *et al*. recently found that low-anxious subjects showed an increased activation in the fronto-parietal networks, while highly anxious individuals showed a particular pattern of increased functioning of the cingulo-opercular and ventral attention favoring attention deficits [12]. In this study we did no found correlations between the severity of anxiety and verbal fluency but lower scores were found related to older age before treatment, in both semantic and phonemic verbal fluency. This finding suggests that anxiety may affect differently cognitive functions according age.

Limitations of this study must be mentioned: In this observational study we did not included a parallel control group, which is not allowed in a phase IV trial with highly symptomatic patients with inherent risks. Indeed, we could not compare the learning curve to determine the cognitive differences before and after treatment.

Cognitive tests were retested periodically during all the treatment period, principally to detect cognitive adverse events, nevertheless in this study we analyzed only at basal and at 12 weeks to determine the relationship within the clinical variables inside each period (basal: anxiety without treatment, and 12 weeks with alprazolam treatment).

5. Conclusions

In this study older age factor was associated with verbal fluency impairment in GAD patients.

Stratified treatments analyzing age and sex factors, including allostatic load measurements and cognitive assessments may be useful tools to determine the

effectiveness and the safety of psychopharmacological treatments.

Acknowledgements

This study was funded with a partial grant from Gador SA, Buenos Aires and partial funds of the Henri Laborit Institute of Biosciences, Córdoba, Argentina. We want to thank Patricia Solís for her help in the study.

Conflicts of Interest

CAS and LD received a partial grant from Gador SA, Darwin 429, Buenos Aires City, Argentina. EJAR in an investigator employed by Gador SA. CR does not declare any conflict of interest.

Patient Consent

Obtained. All patients signed the informed consent for participating in this study.

Ethics Approval

An Independent Ethics Committee of FEFyM (Fundación de Estudios Farmacológicos y Medicamentos/Foundation for Pharmacological Studies and Drugs, Buenos Aires), and regulatory authorities of Argentina (ANMAT, Dossier # 61409-8 of 20 April 2009), approved the protocol, following the law of Habeas Data and psychotherapeutic drug control.

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