Imipramine for vestibular dysfunction in panic disorder

A prospective case series

Marco Andre Mezzasalma[1], Kátia de Vasconcellos Mathias[1],
Isabella Nascimento[1], Alexandre M. Valença[2], Antonio E. Nardi[1]

ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy and effectiveness of imipramine on the treatment of comorbid chronic dizziness and panic disorder. **Method:** Nine patients with panic disorder and agoraphobia associated with chronic dizziness underwent otoneurological screening and were treated with a 3-months course of imipramine. Anxiety levels were measured with the Hamilton Anxiety Scale (HAM-A), dizziness levels were evaluated using the Dizziness Handicap Inventory (DHI), and panic severity and treatment outcome were assessed with the Clinical Global Impression Scale (CGI). **Results:** At the baseline 33.3% (n=3) had a bilateral peripheral deficit vestibulopathy, the mean scores for HAM-A were 27.2±10.4, for DHI were 51.7±22.7, and for CGI-S were 4.8±0.9. All patients had a significant reduction in their HAM-A (11.1±5.5, p=0.008), DHI (11.5±8.1, p=0.008) and CGI-I (1.8±0.7, p=0.011) levels after 3-months imipramine treatment (mean=72.2±23.2 mg/day). **Conclusion:** This study found a decrease in anxiety levels and in the impact of dizziness in the patients' quality of life after a 3-months treatment course with imipramine.

Key words: dizziness, panic disorder, imipramine, anxiety disorders.

Imipramina para disfunção vestibular em transtorno do pânico: uma série de casos prospectiva

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a eficácia e efetividade da imipramina no tratamento da tontura crônica e do transtorno de pânico comórbidos. **Método:** Nove pacientes com transtorno do pânico e agorafobia associada com tontura crônica foram submetidos à avaliação otoneurológica e tratados durante 3 meses com imipramina. Os níveis de ansiedade foram medidos através da Escala Hamilton de Ansiedade (HAM-A); os de tontura foram avaliados usando o *Dizziness Handicap Inventory* (DHI), e a gravidade do pânico e sua resposta pela Escala de Impressão Clínica Global (CGI). **Resultados:** Na avaliação inicial, 33,3% (n=3) da amostra apresentavam vestibulopatia periférica deficitária bilateral; as médias foram: da HAM-A 27,2±10,4, do DHI 51,7±22,7 e do CGI-S 4,8±0,9. Todos tiveram uma redução significativa nos escores de HAM-A (11,1±5,5, p=0,008), DHI (11,5±8,1, p=0,008) e CGI-I (1,8±0,7, p=0,011), após 3 meses de tratamento com imipramina (média=72,2±23,2 mg/dia). **Conclusão:** Este estudo encontrou uma diminuição dos níveis de ansiedade e do impacto da tontura na qualidade de vida dos pacientes após um curso de 3 meses de tratamento com imipramina.

Palavras-chave: tontura, transtorno de pânico, imipramina, transtornos de ansiedade.

Correspondence
Marco A. Mezzasalma
Rua Visconde de Pirajá 414 / 701
22410–003 Rio de Janeiro RJ - Brasil
E-mail: mmezza@uol.com.br

[1]Panic and Respiration Laboratory, Psychiatric Institute of the Federal University of Rio de Janeiro, Rio de Janeiro RJ, Brazil;
[2]Federal Fluminense University, Niterói RJ, Brazil.

Dizziness is one of the most common complaints in clinical practice. In the absence of rotational vertigo, dizziness has been considered another somatoform symptom common to anxiety disorders[1].

Psychiatric disorders have been associated with chronic dizziness in the so-called idiopathic dizziness[2], and different studies have shown that patients that suffer from acute vestibular conditions often develop psychiatric disorders[3,4].

Patients with anxiety disorders have a higher rate of peripheral vestibular dysfunction compared to control populations, especially in panic disorder with agoraphobia[5]. Cochleovestibular dysfunction appears to have a bidirectional connection with psychiatric disorders[6]. The panic disorder can be superimposed on chronic vestibulopathy, and psychiatric patients with a cochleovestibular lesion have diminished chances for complete recovery[6].

There are many difficulties in the evaluation of patients with vestibular dysfunctions and comorbid psychiatric disorders, and the examination of these patients is very time consuming and requires much more empathy than does examination of patients with a normal mental state[6]. There is also the need of a multidisciplinary evaluation of these patients, since anxiety can lead to somatic and behavioral symptoms or to the worsening of a vestibular symptom.

Dizziness is one of the symptoms of panic attacks, as are palpitations, shortness of breath and chest pain or discomfort, but psychiatrists usually do not refer panic disorder patients for otoneurologic evaluations as they refer them to cardiologic evaluations. This lack of adequate evaluation may lead patients away from an adequate diagnosis and treatment[7].

There are few studies using imipramine on the treatment of chronic dizziness associated with panic disorder. Imipramine is a tricyclic antidepressant with a low cost and easy availability, and has effectiveness and safety well documented on the treatment of panic disorder[8].

The purpose of this study was to evaluate the efficacy and effectiveness of imipramine on the treatment of comorbid chronic dizziness and panic disorder.

METHOD
Subjects

Fifteen patients were consecutively recruited at the out-patient facility of the Panic and Respiration Laboratory at the Psychiatric Institute of the Federal University of Rio de Janeiro, Brazil. Participants were men and women, aged between 18 and 60, who met DSM-IV criteria for panic disorder, with or without agoraphobia, determined by the Mini International Neuropsychiatric Interview version 5.0, Brazilian version[9]. Patients needed to have a minimum of four panic attacks, at least one of

which was unanticipated, during the 4 weeks before the initiation of the otoneurological evaluation. All patients also reported dizziness, defined as persistent (i.e. at least three months) sensations of nonvertiginous dizziness, light-headedness, heavy-headedness or subjective imbalance present on most days.

Our inclusion criterion was the presence of dizziness not solely during panic attacks[10], and the exclusion criteria were: evidence of chronic otitis media; prior use of ototoxic drugs and/or chemotherapy, a clinical history of true rotational vertigo, concomitant treatment with any psychotropic drug or psychotherapy during the study, use of any regular antipsychotic, antidepressant, regular benzodiazepine or nonbenzodiazepine anxiolytic medication within 4 weeks, or use of fluoxetine within 5 weeks of the first administration of study medication, or the presence of suicidal risk. Women of childbearing potential had to be using an effective method of birth control. Pregnant or nursing women were excluded from participation.

After complete description of the study to the subjects, written informed consent was obtained. The protocol complying with the principles laid down in the Declaration of Helsinki was approved by the Ethics Committee of the Institute of Psychiatry from the Federal University of Rio de Janeiro.

Procedure

All patients underwent a full otoneurological examination with an otorhinolaryngologist to detect spontaneous, positional and positioning nystagmus (using Dix–Hallpike and McClure maneuvers), including the head-shaking and head-thrust tests[11,12]. Positional nystagmus was recorded in the supine position, with the head straight, head turned to the left and right side, and head hanging down. Nystagmus in darkness with a slow phase velocity of less than 38/second was considered insignificant[11,12].

Examination of the oculomotor system (i.e. smooth pursuit and saccades) was also performed. In the same session, patients underwent caloric stimulation as proposed by Freyss (i.e. 125 ml of water, 30° and 44° in 30 seconds)[13]. Evaluation of the ocular movements was carried out using a vectoelectronystagmography (SCE Nistagmus - Sistema Computadorizado para Eletronistagmografia, version 5.1, Contronics, RS, Brazil) while bithermal caloric testing was performed with an otocalorimeter (E96 Água - Estimulador Otoneurológico a Água, Contronics, RS, Brazil). We used angular slow phase velocity, as calculated during 10 seconds of culmination, as the single parameter of labyrinthine function. Data were interpreted in terms of directional preponderance and unilateral weakness, which were considered significant when greater than 30 and 25 per cent, respec-

tively. When total slow phase velocity was less than 20º/second, stimulations were considered hyporesponsive, and hyper-responsive when greater than 140º/second[11,12]. We considered central signs to comprise at least one of the following findings: [1] disorganized pursuit and reduction of pursuit gain; [2] saccades dysmetria with undershoot, overshoot, or asymmetrical latency or velocity; [3] rebound nystagmus; [4] visual fixation suppression of nystagmus of less than 60 per cent; [5] pure vertical or torsional spontaneous or positional nystagmus; or [6] positional nystagmus when bilateral, beating to the uppermost or lowermost ear, showing no latency, low frequency, lack of fatigability and habituation, without concomitant vertigo[14,15].

The otoneurological evaluations were conducted before the initiation of treatment with imipramine, and were repeated after three months of treatment with imipramine. All patients also had laboratorial exams (complete blood count, cholesterol and triglycerides levels, glycemia, and electrolytes (Na^+, K^+, Ca^{++}, Cl^-, and Mg^{++}) to exclude any possible metabolic causes for the dizziness complaint before treatment begun.

The severity of anxiety was measured using the Hamilton Scale for Anxiety (HAM-A)[16], and the severity of dizziness was measured by the 25-item Dizziness Handicap Inventory scale (DHI), which generated a total score (range zero to 100) which indicated the patient's self-perceived level of handicap associated with their dizziness[17]. Global severity of panic disorder was evaluated with the Clinical Global Impression Severity Scale (CGI-S, ranging from 1 - not at all ill to 7 - extremely ill)[18]. Global change from the baseline assessment was rated by means of the Clinical Global Impression Improvement Scale (CGI-I, ranging from 1 - very much improved to 7 - very much worse)[18].

All patients were evaluated with the HAM-A, DHI and CGI-S before treatment with imipramine (baseline) and were evaluated with the HAM-A, DHI and CGI-I after three months of treatment.

Treatment with imipramine was instituted with a beginning dose of 25 mg/day, increased to 50 mg/day after four days. Afterwards de dose of imipramine used was adjusted based on the patient's anxiety symptoms and on the frequency of panic attacks.

Statistical analyses

The Statistical Package for Social Sciences (IBM SPSS Statistics), version 18.0 was used to perform the statistical analysis. Quantitative variables were expressed as means±standard deviation. The median, 25th and 75th percentiles of the rating scales are expressed graphically. We used the Wilcoxon Signed Ranks Test to compare the scores of the scales before and after treatment with imipramine. P-values<0.05 were considered statistically significant.

RESULTS

From the 15 initial patients enrolled in this study we had to exclude 6 patients: four of these patients completed the baseline evaluation and never returned to begin the imipramine treatment, one patient was excluded from the study due to intolerance to imipramine side effects (constipation) and one patient developed a major depressive episode with suicide ideation after baseline evaluation.

We included in the study 9 patients with a psychiatric diagnosis of panic disorders with agoraphobia, 8 women (88.9%) and 1 man (11.1%), with a mean age of 33.7±5.1 years. All patients also reported dizziness, defined as chronic (i.e. at least three months) sensations of nonvertiginous dizziness, light-headedness, heavy-headedness or subjective imbalance present on most days.

Table 1. Sociodemographical, comorbidities and psychiatric family history data of the 9 patients with panic disorder and chronic dizziness treated with imipramine.

Patient	Gender	Age	Marital status	Comorbidities	Family history
1	Female	37	Married		No
2	Female	33	Married		No
3	Male	34	Single	SP and OCD	Suicide (Grandmother's sister)
4	Female	36	Married	MDE	No
5	Female	40	Married	MDE	No
6	Female	29	Married		No
7	Female	24	Single		No
8	Female	31	Married		No
9	Female	39	Married	MDE, SP and PTSD	No

SP: social phobia; OCD: obsessive-compulsive disorder; MDE: major depressive episode; PTSD: post-traumatic stress disorder.

Table 2. Clinical variables in 9 panic disorder patients with chronic dizziness at baseline and after 3 months of treatment with imipramine.

Patient	HAM-A[1]	DHI[1]	CTCS[1]	CGI-S[1]	HAM-A[2]	DHI[2]	CTCS[2]	CGI –I[2]
1	14	38	Normal	5	7	8	Normal	2
2	31	24	Normal	5	23	10	Irritative	1
3	32	20	Bilateral deficit	4	15	2	Normal	2
4	31	92	Normal	6	11	4	Normal	1
5	26	56	Normal	3	10	22	Normal	3
6	35	50	Bilateral deficit	5	7	6	Normal	1
7	11	58	Normal	5	5	26	Normal	2
8	21	54	Bilateral deficit	6	8	10	Normal	1
9	44	74	Normal	5	14	16	Normal	2

HAM-A: Hamilton Scale for Anxiety; DHI: Dizziness Handicap Inventory; CTCS: results for Caloric Tests and Central Signs; CGI-S: Clinical Global Impression Severity Scale; CGI-I: Clinical Global Impression Improvement Scale; [1]Before treatment with imipramine; [2]After 3 months treatment with imipramine.

The patients' sociodemographical, comorbidity and psychiatric family history data can be seen in Table 1. All patients had panic disorder with agoraphobia, and 44.4% (n=4) of the sample had other psychiatric comorbidities, being the most frequent major depressive episode in 33.3% of the sample (n=3). Only one patient had a psychiatric family history of suicide.

The results of the vectoelectronystagmography and the HAM-A, DHI, and CGI scales at the baseline and after three months of treatment with imipramine can be seen on Table 2. There were no otoneurological abnormalities on the physical exams, and there were no alterations on the laboratorial exams of any of the patients.

At the baseline evaluation, 33.3% (n=3) of the sample had a bilateral peripheral deficit vestibulopathy, the mean HAM-A levels were 27.2±10.4, the mean DHI levels were 51.7±22.7 and the mean CGI-S levels were 4.8±0.9.

Treatment with imipramine had doses between 50 and 100 mg/day, with a mean of 72.2±23.2 mg/day, during three months.

The only finding at the vectoelectronystagmography was a result of bilateral peripheral irritative vestibulopathy on a patient that had a normal baseline result, and all three patients that had bilateral peripheral deficit vestibulopathy at baseline evaluation had normal exams.

We found a statistically significant reduction in the mean HAM-A levels (11.1±5.5, p=0.008), in the mean DHI levels (11.5±8.1, p=0.008) and in the mean CGI-I levels (1.8±0.7, p=0.011). We also present the median and the 25 and 75 percentiles of the results of the HAM-A, DHI, and CGI scales at the baseline and after three months of treatment with imipramine on Fig 1, Fig 2 and Fig 3, respectively.

No patient had panic attacks in the previous two weeks, and the clinical improvement was also significative. All patients had also fully remitted from their agoraphobia.
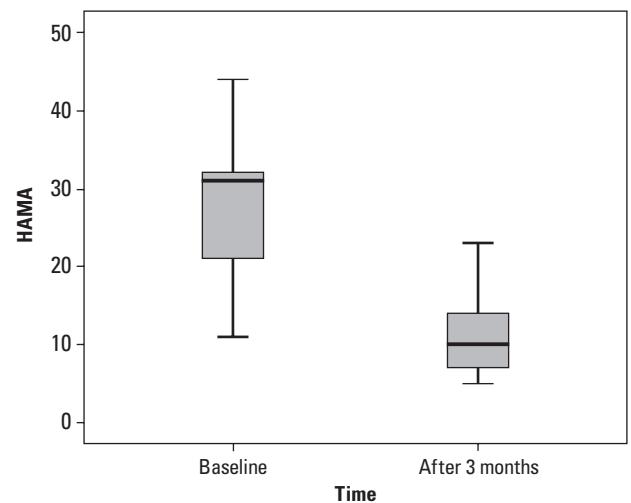
Fig 1. Median, 25 and 75 percentiles of the HAM-A scores of our 9 patients sample at baseline and after 3 months of treatment with imipramine.
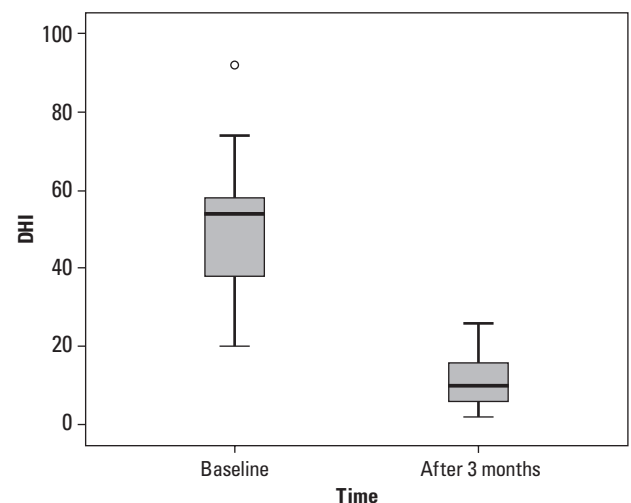
Fig 2. Median, 25 and 75 percentiles of the DHI scores of our 9 patients sample at baseline and after 3 months of treatment with imipramine.
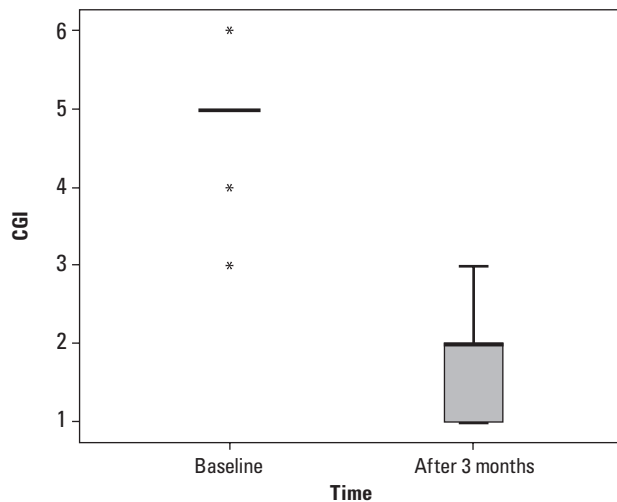
Fig 3. Median, 25 and 75 percentiles of the CGI scores of our 9 patients sample at baseline and after 3 months of treatment with imipramine.

DISCUSSION

In this study we have found 33.3% of peripheral vestibular alteration in patients with panic disorder and agoraphobia with chronic dizziness, a number that is similar to data found in the literature[19,20].

We also found a significant decrease in anxiety levels, in the impact of dizziness in the patients' quality of life and improvement in the severity of the panic disorder after a 3-months treatment course with imipramine.

In spite of the statistical significance found, these data should be interpreted carefully, since one limitation of our study is the small size of our sample. Our out-patient unit is a specialized center for the diagnosis and treatment of panic disorder and we receive few patients with chronic dizziness complaints without panic symptoms. Few patients with chronic dizziness first seek psychiatric evaluation, and this limited our patients' recruitment.

The small sample of this study also forbids us to make any considerations on the hypothesis that, in patients with panic disorders, the symptom of dizziness may not be a 'functional' symptom related to an anxiety state but may instead be linked to malfunction of the vestibular system.

There are theories that the vestibular system may also act as a trigger on the homeostatic stability of patients with panic disorder and may influence the onset or the maintenance of panic disorder[20]. Also there are theories that vestibular input may affect panic disorders due to alterations on the serotoninergic system[7].

Serotoninergic pathways departing from the nucleus raphe have been demonstrated to play an important role in anxiety processing in rats[21]. According to the fear circuit theory, the amygdala and periaqueductal grey circuit are important areas in the expression of conditioned fear and avoidance, and there is increasing evidence of possible activation of these circuits in panic disorders with agoraphobia[22,23].

The selective serotonin reuptake inhibitors are currently considered to be the first-line therapy for anxiety disorders[23]. A review about chronic dizziness found these drugs, in a series of open label prospective studies, to be effective in the treatment of chronic dizziness[24]. They also found that roughly 20% of patients were intolerant of these medications[24].

Simon et al.[25] did a prospective pilot study using fluoxetine for vestibular dysfunction and anxiety, where they treated five patients with vestibular dysfunction but no primary anxiety disorder, although all patients had a significant level of anxiety at baseline. All patients had impairment due to dizziness measured by the DHI scale (baseline: mean 30.2, range 14-42) and all patients completed a 12 week course of fluoxetine treatment, with reductions in the HAM-A and DHI scores, which were the primary outcome measures.

Imipramine is a tricyclic antidepressant with serotoninergic activity and has both advantages and disadvantages. Its main advantages are efficacy and efficiency in the treatment of panic disorder, with low cost and good availability. Its main disadvantages are side effects profile and discontinuation due to intolerance. In Brazil cost is still a limiting factor in the treatment of our patients.

Our results are limited due to the size of our patient's sample. Nevertheless, we present this case series in a attempt to further expand the knowledge of treatment options to this frequent comorbidity between anxiety disorders, mainly panic disorder, and chronic dizziness.

Dizziness still presents as a clinical challenge and the majority of the diagnosis are unconclusive and only 10% of all cases have a clear etiology diagnosed, even after a series of expensive exams[26]. The diagnosis and treatmentof patients with vestibular complaints must be approached with a multidisciplinary evaluation, and all treatment options must be considered. Since vestibular symptoms can aggravate psychiatric symptoms and psychiatric disorders can complicate even further the evaluation of patients with dizziness, every therapeutic option available must be considered, and imipramine and other tryciclic medications must be considered viable options.

REFERENCES

1. Nedzelski JM, Barber HO, McIlmoyl L. Diagnoses in a dizziness unit. J Otolaryngol 1986;15:101-104.
2. Simon NM, Pollack MH, Tuby KS, Stern TA. Dizziness and panic disorder: a review of the association between vestibular disfunction and anxiety. Ann Clin Psychiatric 1998;10:75-80.
3. Gurgel JDC, Costa KVT, Cutini, FN, Sarmento KMAS, Mezzasalma MA, Cavalcanti HVR. Dizziness associated with panic disorder and agoraphobia: case report and literature review. Rev Bras Otorrinolaringol 2007;3: 569-572.
4. Pollak L, Klein C, Stryjer R, Kossich V, Rabey JM. Anxiety in the first attack of vertigo. Otolaryngol Head Neck Surg 2003;128:829-834.

5. Furman JM, Redfern MS, Jacob RG. Vestibulo-ocular function in anxiety disorders. J Vest Res 2006;16:209-215.

6. Szirmai A, Kisely M, Nagy G, Nedeczky Z, Szabados EM, Tóth A. Panic disorder in otoneurological experience. Int Tinnitus J 2005;11:77-80.

7. Staab JP, Ruckenstein MJ. Which comes first? Psychogenic dizziness versus otogenic anxiety. Laryngoscope 2003;113:1714-1718.

8. Kumar S, Malone D. Panic disorder. Clin Evid (Online). 2008;pii: 1010.

9. Amorim, P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. Rev Bras Psiquiatr 2000;22:106-115.

10. Staab JP. Chronic dizziness: the interface between psychiatry and neuro-otology. Curr Opin Neurol 2006;19:41-48.

11. Torok N. Quantitative parameters in nystagmography. ORL J Otorhinolaryngol Relat Spec 1974;36:37-45.

12. Barber HO, Stockwell CW. Manual of Electronystagmography. St Louis, Missouri: Mosby, 1980.

13. Freyss G, De Saint-Macary M, Henin JM. L'expression graphique des épreuves vestibulaires caloriques. Ann Otolaryngol Chir Cervicofac 1973;90:745-761.

14. Jacobson GP, Henry KG. Effect of temperature on fixation suppression ability in normal subjects: the need for temperature and age-dependent values. Ann Otol Rhinol Laryngol 1989;98:369-372.

15. Brandt T. Positional and positioning vertigo and nystagmus. J Neurol Sci 1990;95:3-28.

16. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50-55.

17. Castro ASO, Gazzola JM, Natour J, Ganança FF. Versão Brasileira do Dizziness Handicap Inventory. Pró-Fono R Atual Cient 2007;19:97-104.

18. Guy W (Ed). ECDEU Assessment manual for psychopharmacology, revised. DHEW Publication. Superintendent of Documents, Government Printing Office, Washington, DC, 1976.

19. Jacob RG, Redfern MS, Furman JM. Space and motion discomfort and abnormal balance control in patients with anxiety disorders. J Neurol Neurosurg Psychiatry 2009;80:74-78.

20. Teggi R, Caldirola D, Colombo B, Perna G, Comi G, Bellodi L, Bussi M. Dizziness, migrainous vertigo and psychiatric disorders. J Laryngol Otol 2009;3:1-6.

21. Dos Santos L, de Andrade TG, Zangrossi H Jr. Serotonergic neurons in the median raphe nucleus regulate inhibitory avoidance but not escape behavior in the rat elevated T-maze test of anxiety. Psychopharmacology (Berl) 2005;179:733-741.

22. Mezzasalma MA, Valença AM, Lopes FL, Nascimento I, Zin WA, Nardi AE. Neuroanatomy of panic disorder. Rev Bras Psiquiatr 2004;26:202-206.

23. Zanoveli JM, Ferreira-Netto C, Brandão ML. Conditioned place aversion organized in the dorsal periaqueductal gray recruits the laterodorsal nucleus of the thalamus and the basolateral amygdala. Exp Neurol 2007; 208:127-136.

24. Ruckenstein MJ, Staab JP. Chronic subjective dizziness. Otolaryngol Clin North Am 2009;42 :71-77.

25. Simon NM, Parker SW, Wernick-Robinson M, et al. Fluoxetine for vestibular dysfunction and anxiety: a prospective pilot study. Psychosomatics 2005;46:334-339.

26. Kroenke K, Lucas C, Rosemberg ML, et al. Causes of persistent dizziness: A prospective study of 100 patients in primary care. Ann Intern Med 1992;177:898-904.