

Fluoxetine for Vestibular Dysfunction and Anxiety: A Prospective Pilot Study

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Anxiety states and disorders amplify the symptoms and impairment associated with vestibular dysfunction. Five patients with inner ear vestibular dysfunction and anxiety were prospectively treated with fluoxetine, 20–60 mg/day, and received an extensive battery of assessments at baseline and after 12 weeks of treatment. Fluoxetine led to significant or near significant reductions in anxiety measures and in impairment due to dizziness; improvements in clinical balance function and vestibular function were less clear. The data add to the literature suggesting a role for selective serotonin reuptake inhibitors in the treatment of dizziness and anxiety.

(Psychosomatics 2005; 46:334–339)

The overlap of dizziness and balance system disorders with anxiety, although yet to be fully understood, has received substantial interest in the scientific literature.¹ Recently described potential neurobiological pathways^{2,3} may help explain the high prevalence of comorbid anxiety with dizziness, and specifically dizziness due to vestibular dysfunction.⁴ Anxiety states and disorders appear to amplify symptoms of vestibular dysfunction,⁵ with additive functional limitations associated with the comorbid psychiatric difficulties.⁶ Two studies of healthy subjects have demonstrated the interaction between anxiety and vestibular symptoms. In the first, elevated anxiety or other mood states predicted a poorer ability to utilize sensory inputs to the vestibular system to maintain balance.⁷ In the second, higher levels of anxiety were associated with greater postural sway, with the relationship hypothesized to be occur-

ring at the level of the interaction between visual inputs and vestibular and somatosensory inputs.⁸ Clinical experience suggests that many patients experiencing dizziness also experience anxiety symptoms that may not reach threshold criteria for a DSM-IV diagnosis or may be secondary to vestibular pathology. It should be noted that the term “vestibular dysfunction,” as used throughout this manuscript, describes a syndrome that consists of subjective symptoms of dizziness—which may include vertigo, motion sickness, nausea, and anxiety—that may occur spontaneously or be reproduced with changes of head and body position. Patients may or may not have objective abnormalities of the vestibuloocular reflexes and vestibulospinal reflexes. While an adequate discussion of the etiology of the syndrome is beyond the scope of this article, the etiology for the purposes of this study was limited to abnormalities in the vestibular organs of the ear. Patients with brainstem or cerebellar vestibular abnormalities were excluded. While some patients may experience dizziness of psychogenic origin,⁹ resolving ongoing debate about the psychological versus vestibular origin of symptoms in some patients is not the focus of this article, and patients

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with psychogenic dizziness were not specifically recruited. This article uses the term vestibular dysfunction to refer to the syndrome of inner ear vestibular hypofunction that may or may not be amplified in the presence of anxiety or other psychological reactions to the syndrome.

Behavioral models explaining the overlap of dizziness and anxiety components are fairly well established,⁵ with preliminary evidence presented for efficacy of both vestibular rehabilitation and cognitive behavioral interventions.^{9,10} Less data are available to support pharmacotherapy for vestibular dysfunction and anxiety. Medications such as meclizine may provide some initial relief but mask the ability of the central nervous system to compensate for the vestibular loss. Benzodiazepines have been employed specifically for patients with complaints of dizziness and anxiety, but many patients do not respond to these interventions either initially or in the long term.¹¹ Thus, although clinicians may employ behavioral therapy or pharmacotherapy in attempts to alleviate symptoms, there are currently no established treatments for coexisting vestibular dysfunction and anxiety.

Previous data suggest that agents modulating the serotonergic system, such as the selective serotonin reuptake inhibitor (SSRI) fluoxetine, may be effective in patients with dizziness, inner ear vestibular dysfunction, and anxiety symptoms.⁴ Modulation of serotonin is of interest because of recent support for a role of serotonin in the neurobiology of fear and vestibular pathways.^{2,3,12–19} To our knowledge, there has been only one prior study, a retrospective case review, of SSRI pharmacotherapy in patients with significant dizziness.¹¹ In this study, patients with major depression or anxiety disorder ($N=41$) or those with psychiatric symptoms or “minor” disorders such as specific phobia ($N=19$), of whom a minority had dizziness due to an otoneurologic condition, were assessed with the Clinical Global Impression (CGI) improvement scale.¹¹ Sixty-three percent ($N=38$) of patients were much or very much improved after 20 weeks of treatment, while 25% were intolerant of even a slow titration of the SSRI. SSRIs are standard care for anxiety disorders.²⁰ While SSRIs have been identified as a potentially beneficial pharmacological treatment of vestibular dysfunction,² it remains unclear whether such an effect would be mediated by an impact on psychological reactions to dizziness, the central processing of vestibular information (regardless of whether the vestibular lesion is peripheral or central), or a direct impact on peripheral vestibular function, although a combination of the first two seems most likely. Regardless, SSRIs are currently not widely used for vestibular dysfunction.²¹ More

data are needed to understand the role of SSRIs in specific elements of these disorders.

The aim of this pilot study was to prospectively and systematically examine the efficacy, tolerability, and impact on functioning of the SSRI fluoxetine on both anxiety and dizziness due to inner ear vestibular dysfunction. In addition, we directly examined the impact of treatment with fluoxetine on measures of vestibular and balance function. Our hypothesis was that treatment with fluoxetine would significantly reduce anxiety and associated impairment in self-reported measures of functioning due to dizziness without substantially altering tests of vestibular and balance function.

METHOD

Men and women aged 18 to 75 with dizziness due to vestibular dysfunction and associated anxiety symptoms were recruited through advertisement and clinical referral. The diagnosis of a syndrome of peripheral vestibular dysfunction (i.e., inner ear vestibular hypofunction) was confirmed by the study otoneurologist (S.W.P.) after reviewing the patient's history and results of a vestibular test battery, which included electronystagmography, sinusoidal vertical axis rotation, visual-vestibular interaction rotation testing, and posturography performed at baseline or within the preceding 6 months. However, clear abnormalities on the vestibular test battery were not specifically required if the history and presentation were consistent with a syndrome of peripheral vestibular dysfunction. A minimum score of 10 on the Hamilton anxiety scale was required for entry.

Because this was a study of associated anxiety symptoms and not specifically an anxiety disorder, patients with primary DSM-IV axis I psychiatric diagnoses, with the exception of mild to moderate major depression and dysthymia (Hamilton depression scale score <18), as determined with the Structured Clinical Interview for DSM-IV (SCID), were excluded. Patients with a history of alcohol or substance use or dependence within the preceding 6 months, or positive toxicology screen results for drugs of abuse at baseline, were also excluded. The use of concomitant psychoactive medications (e.g., benzodiazepines, antidepressants) within 2 weeks of baseline was prohibited, as were specific vestibular treatments such as meclizine or vestibular physical therapy within 1 week of baseline and throughout the study.

This study was approved by the institutional review board at the Massachusetts General Hospital. All participants signed written informed consent. Fluoxetine was ini-

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tiated at 10 mg/day at baseline with flexible upward titration at weekly to biweekly study visits, following analysis of efficacy and tolerability, to a maximum of 60 mg/day for a total of 12 weeks.

We obtained baseline and endpoint measures of anxiety (Hamilton anxiety scale), fear of physical sensations (Anxiety Sensitivity Index), depression (Hamilton Depression Rating Scale), and functional limitations due to dizziness (Dizziness Handicap Inventory²²). The Dizziness Handicap Inventory is a 25-item, self-rated measure that utilizes a 0 to 2 severity scale to measure self-perceived handicapping effects of vestibular disease, including functional, physical, and emotional effects. The Dizziness Handicap Inventory has high established test-retest reliability and good internal consistency.²² The Anxiety Sensitivity Index is a self-rated, 16-item scale that measures fears of physical sensations and cognitive loss of control on a 0 to 4 severity scale, with high internal consistency and a normative mean of 19.^{23,24} The primary outcomes for this study were the scores on the Hamilton anxiety scale and the Dizziness Handicap Inventory. Study participants also underwent baseline and endpoint testing of their functional gait and balance. Clinical balance measurements consisted of a detailed examination of static postural control, dynamic postural control, and gait speed. A clinical measurement of the vestibular ocular reflex was also ad-

ministered. Static postural control was examined by using the modified Clinical Test of Sensory Integration and Balance.²⁵ Dynamic postural control was examined with the use of the Dynamic Gait Index²⁶ and tandem gait with eyes open and eyes closed (originally described by Fregly et al. as a useful addition to their original ataxia test battery²⁷). Last, the timed "up and go" test,²⁸ including timed "up and go" with a cognitive task,²⁹ was used to measure gait speed and the ability to divide attention during gait, respectively. All clinical gait and balance measures are standardized tests that have been validated for patients with vestibular dysfunction.²⁶

All statistical tests were paired t tests, with significance set at the 0.05 level.

RESULTS

Five patients (four men and one woman; mean age = 49.4 years [SD = 13.6]) participated in this pilot study (see Table 1 for vestibular diagnoses and vestibular test results). The mean duration of vestibular dysfunction was 7.0 years (range = 0.75 to 24 years). Although no patient met criteria for a primary anxiety disorder, all patients had a clinically significant level of anxiety at baseline (Table 2). One patient had vertigo-associated panic attacks and avoidance (subject 3), while the other four all reported subsyndromal

TABLE 1. Vestibular Diagnosis and Vestibular Function Test Results at Baseline and Endpoint for Five Patients Reporting Dizziness and Symptoms of Anxiety

Patient	Vestibular Diagnosis	Vestibular Test Abnormalities	
		Baseline	Endpoint
1	Bilateral vestibular hypofunction or compensated unilateral lesion (status post gentomycin toxicity)	Sinusoidal vertical axis rotation: mildly decreased gains, increased phase leads and reduced time constant Posturography: excessive sway on sway referenced platform	Sinusoidal vertical axis rotation: improved time constant Posturography: improved to normal
2	Vestibular lesion with good central nervous system compensation (status post shingles)	Electronystagmogram: severely reduced right caloric response Sinusoidal vertical axis rotation: decreased low frequency gain and increased low frequency phase leads Posturography: normal	Slight improvement right caloric response and new positional nystagmus Sinusoidal vertical axis rotation: no change Posturography: excessive sway fixed platform
3	Chronic unilateral vestibular dysfunction (24 years) of unclear etiology	Sinusoidal vertical axis rotation: left preponderance rotation induced nystagmus Posturography: excessive sway on fixed platform	Posturography: improved to normal
4	Clinical syndrome of vestibular damage (status post viral labyrinthitis)	None	Not repeated (normal baseline)
5	Incompletely compensated fixed peripheral unilateral vestibular lesion (status post viral illness with vestibular neuronitis)	Sinusoidal vertical axis rotation: phase shift and asymmetrical response	Sinusoidal vertical axis rotation: persistent phase shift but resolution of asymmetry of response

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symptoms themselves and possibly for reducing the intensity and associated distress of dizziness, thus permitting improvement in function despite ongoing vestibular symptoms.

The role of serotonin in the vestibular system has been supported by animal studies that have demonstrated modification of vestibular neuronal firing in the rat by 5-hydroxytryptamine,^{13–15} suggesting dysregulated serotonergic function may lead to vestibular dysfunction. Serotonin may inhibit sensory response to movement, and deficiencies in serotonergic tone can cause increased sensitivity and excitability of pertinent neurons.¹⁶ Furthermore, dizziness occurring during the serotonin withdrawal syndrome increases with head movement and has been attributed to a temporary deficiency of serotonin.^{17,18} Recently, neural connectivity between the fear network structures—such as the central amygdaloid nucleus, infralimbic cortex, hypothalamus, and parabrachial nucleus—have been described, with the identification of an interconnection of the parabrachial nucleus and vestibular nuclei offering one potential neurobiologic explanation for the association of fear and anxiety states with vestibular pathways.^{2,3} Further, serotonergic pathways have been implicated in this network (with the identification of 5HT_{2a} receptors in vestibular pathways) as well as amygdaloid and cortical targets of the parabrachial nucleus.³

Serotonergic agents such as the selective serotonin reuptake inhibitors have been hypothesized to be effective in panic disorder via a desensitization of the fear network,¹⁹ and they may also serve to dampen the response to abnormal vestibular inputs. Our data provide indirect support for this possibility, since treated patients experienced a significant reduction in their fear of somatic sensations (as measured by the Anxiety Sensitivity Index). Conclusions from this study are limited by the lack of a placebo control condition and the small number of subjects. In addition, we cannot rule out the possibility that subject 4, who did not exhibit abnormalities during testing, may not have had continued vestibular dysfunction but rather a psychologically conditioned sensitivity to motion cues that followed his episode of labyrinthitis; the precise etiology of this clinical presentation remains debated in the literature.^{9,20} However, our data, incorporating a comprehensive set of assessments in a prospectively treated and well characterized group, add to the small but growing literature suggesting a role for SSRIs in the treatment of dizziness and anxiety.

Supported by an investigator-initiated grant from Eli Lilly and Company.

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