

Chronic Dizziness and Anxiety

Effect of Course of Illness on Treatment Outcome

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Objective: To investigate the hypothesis that the efficacy of selective serotonin reuptake inhibitors (SSRIs) for chronic subjective dizziness (CSD) and anxiety depends on the longitudinal pattern of the patients' symptoms.

Design: Prospective cohort study.

Setting: Tertiary care, multidisciplinary, balance center.

Patients: Eighty-eight consecutive patients treated with an SSRI for CSD and anxiety between 1998 and 2003. All patients were referred for evaluation of unremitting dizziness. They entered SSRI treatment after comprehensive neurotologic and psychiatric evaluations revealed a syndrome of CSD with accompanying anxiety. Patients were separated into 3 groups according to their longitudinal patterns of illness: (1) otogenic, defined as primary neurotologic conditions *triggering* secondary anxiety disorders; (2) psychogenic, defined as anxiety disorders alone *causing* dizziness; and (3) interactive, defined neurotologic conditions *exacerbating* preexisting anxiety.

Interventions: Patients with CSD were treated with an SSRI according to an established protocol for at least 8 weeks or until they proved intolerant to medication.

Main Outcome Measures: Changes in dizziness and anxiety as measured by the Clinical Global Impressions–Improvement scale.

Results: Patients with the otogenic and psychogenic patterns of illness had a more complete response to SSRI treatment than did patients in the interactive group ($P < .01$). Rates of SSRI intolerance were similar for all 3 groups.

Conclusions: Selective serotonin reuptake inhibitors are effective for patients with CSD and anxiety. However, patients with clinically significant anxiety preexisting neurotologic illness may require more intensive interventions.

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DESPITE ADVANCES IN NEUROVESTIBULAR testing and diagnostic imaging, the evaluation of patients with the chief complaint of dizziness remains primarily predicated on the clinical history.¹⁻³ Obtaining an accurate history allows the clinician to distinguish among specific symptom complexes that define vestibular and nonvestibular etiologies of dizziness (eg, Ménière's disease, benign positional vertigo, noncompensated vestibular loss, presyncope, and anxiety). Diagnostic testing may be used to support a specific diagnosis, but the clinical history remains preeminent in establishing the cause of the patient's complaints.⁴

Among the various vertiginous and nonvertiginous forms of dizziness is a clinical syndrome of chronic subjective dizziness (CSD) accompanied by anxiety. Patients with this condition describe vague, nonspecific light-headedness and subjective

sensations of imbalance. As opposed to true vertigo or ataxia, they may complain that the inside of their head is spinning or that they are swaying when standing still. These symptoms are pervasive and typically exacerbated in crowded environments with rich visual fields, such as grocery stores and shopping malls. This clinical presentation is often diagnosed as psychogenic dizziness, although recent research suggests that psychiatric illnesses are just as likely to be consequences of dizziness as they are its genesis.⁵⁻⁸

In an effort to understand the relationships between dizziness and psychiatric disorders, we recently studied the longitudinal course of illness in a large cohort of patients (N=132) who presented with CSD and anxiety.⁹ We found 3 equally prevalent subgroups of patients that we called otogenic, psychogenic, and interactive. Patients in the otogenic group had histories of transient or current neuroto-

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logic illnesses (eg, vestibular neuronitis, Ménière's disease), but they developed persistent dizziness and anxiety for the first time after their acute neurotologic event. Patients in the psychogenic group had primary anxiety disorders (eg, panic or generalized anxiety disorder) that presented with prominent dizziness in the absence of any neurotologic illness. Patients in the interactive group had preexisting anxiety disorders or an anxiety diathesis (eg, self-limited periods of excessive worry) without dizziness. The developed chronic dizziness and an exacerbation of their psychiatric condition after they acquired a physical neurotologic illness.

Patients in the otogenic group tended to develop only minor anxiety symptoms (eg, phobic behaviors related just to their dizziness), whereas those in the psychogenic and interactive groups had more serious anxiety disorders (eg, fully developed panic disorder). Psychiatric factors appeared to play an integral role in sustaining patients' dizziness in all 3 groups, regardless of the triggering events. This result was echoed in a recent study,¹⁰ which found that high levels of anxiety in the early aftermath of a bout of vestibular neuronitis predicted a chronic course of dizziness. Thus, the longitudinal history of medical-psychiatric interactions appears to determine the severity and persistence of dizziness and anxiety in this patient population.

In 2 studies,^{11,12} we found that selective serotonin reuptake inhibitors (SSRIs) were effective for patients with chronic dizziness and major or minor anxiety and depression. Similarly, Horii et al¹³ reported that the SSRI paroxetine hydrochloride reduced chronic dizziness and depression. However, all patients did not respond equally well to treatment. Some enjoyed a complete remission of their symptoms, whereas others achieved only partial relief, and 25% were unable to tolerate a therapeutic dose of medication.^{11,12} These results suggest that SSRIs may be an important advance in the treatment of patients with this challenging disorder, but investigations to find clinical predictors of incomplete medication response or intolerance are needed to improve therapeutic outcomes.

We undertook the present study to investigate the hypothesis that the longitudinal patterns of illness (ie, otogenic, psychogenic, and interactive) would predict the efficacy and tolerability of SSRI treatment. We hypothesized that patients with a psychogenic pattern of illness would have a better therapeutic result with SSRIs because these medications are a first-line treatment for the types of anxiety disorders encountered in this group.^{14,15} We also hypothesized that patients with the interactive pattern of illness would be the least tolerant of SSRIs, because common adverse effects of these medications often mimic symptoms experienced by patients with neurotologic illnesses and anxiety (eg, nausea, restlessness, insomnia).

METHODS

CLINICAL EVALUATION

All patients in the study cohort were evaluated by a neurotologist (M.J.R.) and a psychiatrist (J.P.S.). The protocol-driven neurotologic evaluation included a clinical history, physical ex-

amination, audiometric assessment, balance function tests, and magnetic resonance imaging of the head. Patients whose neurotologic examination results demonstrated CSD accompanied by clinically significant anxiety were referred for psychiatric assessment.

Chronic subjective dizziness was identified as follows:

- Persistent (≥ 3 months) sensations of nonvertiginous dizziness, light-headedness, heavy-headedness, or subjective imbalance present on most days;
- Chronic (≥ 3 months) hypersensitivity to one's own motion or to movements of objects in the environment;
- Exacerbation of symptoms in settings with complex visual stimuli (eg, grocery stores) or when performing precision visual tasks (eg, reading, using a computer);
- Absence of active physical neurotologic illnesses, medical conditions, or medications that may cause dizziness;
- Normal radiographic images of the brain; and
- Normal or nondiagnostic findings on balance function tests.

Patients with previous neurotologic illnesses may have had chronic vestibular deficits on balance function test results (eg, patients with previous bouts of vestibular neuronitis whose results showed fully compensated, unilateral caloric weakness). These patients were included in the present study because their physical neurotologic findings could not explain the full extent of their long-standing symptoms (ie, CSD). Furthermore, a previous investigation¹² found that treating such patients with vestibular suppressants (eg, meclizine or benzodiazepines) was ineffective. Clinically significant anxiety symptoms included panic attacks with dizziness or light-headedness, avoidance of situations associated with dizziness, expectations of catastrophic outcomes when dizzy (eg, crashing the car), and excessive worry or chronic anxiety.

In a previous study,¹⁶ the neurotologist's ability to detect these symptoms was validated against a widely used psychiatric questionnaire and a formal psychiatric evaluation. In the present investigation, psychiatric assessments followed the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,¹⁷ which is the standard for psychiatric diagnosis in clinical research.

LONGITUDINAL COURSE OF ILLNESS

The authors independently reviewed patients' longitudinal histories to identify the first episodes of dizziness and the illness(es) responsible for those symptoms. Patients were classified as otogenic, psychogenic, or interactive on the basis of the following criteria.⁹ Patients whose first symptoms of dizziness were caused by physical neurotologic illnesses that were documented in previous medical records or identified retrospectively using strict criteria¹⁻⁴ were classified as otogenic. These patients had no psychiatric history or clinically significant anxiety symptoms predating the onset of dizziness. Patients whose first symptoms of dizziness coincided with clinically significant anxiety, usually panic disorder, were classified as psychogenic. These patients had no histories of vertigo or ataxia, and previous medical records, when available, revealed no physical cause for their symptoms. Patients whose first symptoms of dizziness were caused by physical neurotologic illnesses that were documented in previous medical records or identified retrospectively using strict criteria¹⁻⁴ were classified as interactive. However, these patients had histories of anxiety disorders or a strong anxiety diathesis (eg, anxious temperaments [often described as worrywarts] that predated their dizziness). The physical neurotologic illnesses exacerbated their anxiety, which then sustained sensations of dizziness long after the acute vertiginous events had resolved.

Table 1. Dosing Schedule for Selective Serotonin Reuptake Inhibitors

Drug	Starting Daily Dose, mg	Target Daily Dose by Week 4, mg	Subsequent Daily Increases (2- to 4-wk Intervals), mg	Maximum Daily Dose, mg
Fluoxetine hydrochloride	5-10	20	20	80
Sertraline hydrochloride	12.5-25	50	50	200
Paroxetine hydrochloride	5-10	20	20	60
Citalopram hydrobromide	5-10	20	20	40
Escitalopram oxalate	5	10	10	20

PATIENT SELECTION

Inclusion criteria for this study were (1) male and female patients 18 years and older; (2) a finding of CSD and clinically significant anxiety on neurologic evaluation; (3) diagnosis of a major or minor anxiety disorder on psychiatric assessment; and (4) consensus of the authors on the longitudinal course of illness. Excluded were patients with histories of traumatic brain injuries or autonomic dysregulation (eg, neurocardiogenic [vasovagal] syncope, postural orthostatic tachycardia syndrome, or orthostatic intolerance).

DATA COLLECTION

Data for this study were collected prospectively and abstracted from a research database that was established when our balance center opened in July 1998. Details have been described previously.^{9,12} The database contains anonymous information on all patients who have undergone a psychiatric examination as part of a protocol-driven, multidisciplinary evaluation for dizziness. Database entries have been stripped of all uniquely identifying, personal information. The remaining data include general demographics, presenting symptoms, duration of illness, medical and psychiatric diagnoses (including a designation of the illness first associated with dizziness), treatment histories before referral, therapies prescribed by the authors, and ratings of clinical outcomes. Because the database contains no unique identifying information and is maintained separately from all medical records, the Institutional Review Board at the University of Pennsylvania School of Medicine, Philadelphia, classified this study as exempt from human subjects review.

TREATMENT

Patients were treated with 1 of the 5 SSRIs marketed in the United States at the time of the study (sertraline hydrochloride, fluoxetine hydrochloride, paroxetine, citalopram hydrobromide, or escitalopram oxalate). The initial choice of medication was guided primarily by patient preference and history of SSRI exposure. The dosing schedule is given in **Table 1**.¹² Older patients and those who expressed concern about medication adverse effects started therapy with lower doses. Treatment was continued for a minimum of 8 weeks or until medication intolerance was established. Patients who could not tolerate the first choice of medication were given a second SSRI trial. Those with troubling adverse effects from 2 SSRIs were declared medication intolerant.

OUTCOME MEASURES

Treatment outcomes were rated with the Clinical Global Impressions-Improvement (CGI-I) scale, a clinician-rated instrument that scores changes in patients' overall symptoms: 1 indicating very much improved; 2, much improved; 3, minimally improved; 4,

no change; 5, minimally worse; 6, much worse; and 7, very much worse.¹⁸ The CGI-I is one of the most widely used outcome measures in psychopharmacologic research. Its principal advantages are its simplicity and validated applicability across a wide range of illnesses, including anxiety disorders. In a previous medication trial for patients with chronic dizziness,¹¹ we found that the CGI-I successfully tracked changes in physical symptoms of dizziness, as measured by the Dizziness Handicap Inventory (DHI), and anxiety and depressive symptoms, as measured by standardized psychiatric questionnaires. Specifically, a CGI-I score of 1 corresponded to an end point DHI total score less than 5 and end point psychiatric symptoms in the normal range (ie, complete or nearly complete remission of all symptoms with treatment). A CGI-I score of 2 corresponded to a 50% or greater reduction in both DHI and psychiatric symptom scores (ie, a clinically meaningful improvement in symptoms but not remission). The CGI-I scores of 3 or higher corresponded to minimal changes or worsening of DHI and/or psychiatric symptoms scores. By convention, CGI-I end point scores of 1 or 2 are considered positive outcomes in medication trials. Scores of 3 or higher indicate no clear benefit or worsening with treatment. In the present study, as in our previous clinical trial, CGI-I scores were based on the change in severity of both dizziness and psychiatric symptoms.

STATISTICAL ANALYSIS

Patient demographics, categorical and mean outcome scores, and rates of medication intolerance were compared across the 3 groups. Patient demographics were compared using χ^2 , Fisher exact, and *t* tests as appropriate. Treatment outcomes and rates of medication intolerance were evaluated as follows. The rates of a positive response (CGI-I score of 1 or 2) vs no benefit (CGI-I score of ≥ 3 or medication intolerant) were compared using the χ^2 test to determine the overall treatment outcome. The efficacy of treatment was compared categorically for the intent-to-treat cohort of all 88 patients and for the 72 patients who completed 8 weeks of therapy to determine the categorical outcomes. In this analysis, rates of remission (CGI-I score of 1) vs partial response (CGI-I score of 2) vs no benefit (CGI-I score of ≥ 3 or medication intolerant) were compared using the χ^2 test. The mean CGI-I scores for treatment completers in each group were analyzed with pairwise *t* tests. Rates of medication intolerance were compared using the χ^2 test.

Statistical analyses were performed with the SAS System for Windows, release 8.12 (SAS Institute Inc, Cary, NC). Significance levels were $P < .05$ for all tests.

RESULTS

Of the 88 patients included in this study, 28 had an otogenic pattern, 31 had a psychogenic pattern, and 29 had an interactive pattern of illness. There were 58 women and 30 men with a mean \pm SD age of 41 ± 12 years (age

Table 2. Selective Serotonin Reuptake Inhibitor Treatment Outcome by Pattern of Illness for All Patients

Pattern of Illness	No. of Patients	Positive Response		No Benefit	
		Remission (CGI-I Score of 1)	Partial Response (CGI-I Score of 2)	No Response (CGI-I Score of ≥ 3)	Not Tolerated
Otogenic	28	15	3	4	6
Psychogenic	31	16	7	4	4
Interactive	29	5	13	5	6

Abbreviation: CGI-I, Clinical Global Impressions–Improvement.

Table 3. Mean Improvement for Patients Who Completed Selective Serotonin Reuptake Inhibitor Treatment

Pattern of Illness	No. of Patients	CGI-I Score, Mean \pm SD
Otogenic	22	1.50 \pm 0.80
Psychogenic	27	1.59 \pm 0.84
Interactive	23	2.04 \pm 0.77

Abbreviation: CGI-I, Clinical Global Impressions–Improvement.

range, 18-72 years); 77 (88%) of the cohort were white subjects and 11 (12%) were minority subjects. There were no significant demographic differences between the 3 pattern-of-illness groups.

Table 2 gives the categorical results of SSRI treatment for each group. No differences existed among the 3 groups in overall response rates (ie, positive response vs no benefit) ($\chi^2=2.95$, $P>.57$) or medication intolerance ($\chi^2=2.95$, $P>.64$). However, patients in the interactive group were significantly less likely to achieve full remission and more likely to have a partial response to SSRI treatment. This difference held for both the intent-to-treat ($\chi^2=13.3$, $P<.01$) and completer analyses ($\chi^2=12.9$, $P<.01$).

Table 3 gives the group differences for mean CGI-I scores among patients who completed treatment. The mean response of the interactive group was less robust (higher CGI-I score) than the otogenic ($t=2.32$, $P<.03$) or psychogenic ($t=1.78$, $P<.054$) group, although the latter did not reach statistical significance. There were no differences in rates of remission or mean CGI-I scores between the otogenic and psychogenic groups.

COMMENT

The results of this study show that SSRIs are effective for patients with CSD and anxiety, regardless of the longitudinal pattern of illness. However, the pattern of illness affected the magnitude of response and likelihood of remission. This finding reinforces the preeminence of the clinical history in caring for patients with dizziness. The history informs not only diagnosis but also expectations of treatment outcome.

In keeping with our initial hypothesis, the psychogenic group fared well, which is not surprising given that SSRIs are first-line treatments for panic disorder and generalized anxiety disorder, the 2 most common illnesses in this group.^{14,15} The otogenic group fared equally well,

with a reduction in both dizziness and anxiety. The reasons for this excellent response are not entirely clear, because SSRIs are not typically used to treat the types of phobic symptoms most commonly seen in these patients. It is possible that their low-level anxiety symptoms responded to SSRI treatment, which indirectly improved their dizziness. However, the high percentage of patients with a complete remission of both dizziness and anxiety suggests that the SSRIs may have had a more direct effect on dizziness itself. Serotonin is present in the vestibular nuclei and affects the responsiveness of motion sensitive neural pathways from the vestibular nuclei through the inferior olive to the nodulus and flocculus of the cerebellum.^{19,20} These may be sites where SSRIs can directly decrease dizziness.

Patients in the interactive group did not respond as vigorously to SSRI treatment. Although they experienced a clear reduction in symptoms, significantly fewer patients experienced a full remission compared with the other groups. The long-standing nature of their anxiety diathesis may have limited the extent to which they could benefit from short-term, single-modality therapy. Patients with an interactive pattern of illness may need adjunctive or alternative therapies—pharmacologic, psychotherapeutic, surgical, and rehabilitative—to completely resolve their symptoms. The specific nature of these interventions awaits future research. In contrast to our initial hypothesis, patients in this group were no less tolerant of SSRIs than other patients in the study were.

Limitations of this study include its uncontrolled design (ie, unblinded ratings, open-label medications), the use of 5 different medications in the SSRI class, and a lack of long-term outcome data. Uncontrolled clinical trials may bias results in favor of investigators' hypotheses. In this study, concerns about possible bias are mitigated by the fact that the outcomes did not reflect the initial hypotheses. The excellent therapeutic response experienced by the otogenic group and the equal tolerability of SSRIs across all 3 groups were not anticipated.

Investigators were free to choose among 5 different SSRIs. This provided latitude to individualize therapy for study patients as described in the "Methods" section, but it prohibited conclusions about the benefits of individual medications. However, differential efficacy among the SSRIs has not been convincingly demonstrated in clinical trials for any medical or psychiatric conditions; therefore, none would be expected for chronic dizziness and anxiety.

Outcomes were measured after 8 weeks of therapy, because previous investigations^{11,12} found this to be the

minimum period for an adequate therapeutic trial. We routinely treat patients with SSRIs for 1 year before attempting a slow taper of the medication. However, we do not yet have systematic data on long-term outcomes.

This study found SSRIs to be effective for patients with CSD and anxiety, although not all patients responded equally well to treatment. The magnitude of the therapeutic response depended on the longitudinal pattern of illness, which was determined from the clinical history obtained at the outset of the study. Patients with otogenic and psychogenic patterns had higher rates of complete remission of both dizziness and anxiety during SSRI treatment than did those with an interactive pattern. In contrast, patients in the interactive group were more likely to experience a partial reduction in symptoms rather than a complete remission. These results suggest that neurologists and others who regularly treat patients with chronic dizziness can feel confident recommending SSRI treatment for patients with otogenic and psychogenic patterns of illness. Additional therapies may be needed for those with an interactive pattern of CSD and anxiety.

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