Effects of fluvoxamine on anxiety, depression, and subjective handicaps of chronic dizziness patients with or without neuro-otologic diseases

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Abstract. A prospective, open-label clinical trial was conducted for two aims: first, to evaluate the role of fluvoxamine, one of selective serotonin reuptake inhibitors, in the treatment of dizziness for the first time and to investigate its effective mechanisms. Second, to test the hypothesis that dizziness in patients without abnormal neuro-otologic findings would be induced by psychiatric disorders rather than by unnoticed neuro-otologic diseases. Nineteen patients with neuro-otologic diseases (Group I) and 22 patients in whom standard vestibular tests revealed no abnormal findings (Group II) were treated by fluvoxamine (200 mg/day) for eight weeks. Subjective handicaps due to dizziness using a questionnaire, anxiety and depressive symptoms measured with the Hospital Anxiety and Depression Scale (HADS), and stress hormones (vasopressin and cortisol) were examined before and 8 weeks after treatment. Overall, fluvoxamine decreased subjective handicaps of both Groups I and II. Fluvoxamine decreased HADS of only patients whose subjective handicaps were reduced (= responders) in both groups, suggesting that fluvoxamine was effective for dizziness via psychiatric action rather than a recovery of vestibular function through serotonergic activation. In non-responders of Group II, pre-treatment HADS was higher than in Group I non-responders and it was not decreased by the treatment, suggesting that dizziness of Group II non-responders was due to severe psychiatric disorders rather than unnoticed neuro-otologic diseases. Anxiety and depression components of HADS showed a good correlation at both pre- and post-treatment periods. No post-therapeutic decrease was observed in either vasopressin or cortisol even in responders, suggesting that dizziness was not the sole cause of stress in chronic dizziness patients. In conclusion, patients with or without physical neuro-otologic deficits who report chronic dizziness accompanied by anxiety and depression (as measured by HADS) showed improvements across a full range of subjective handicaps and psychological distress, while patients with physical neuro-otologic defects and minimal anxiety or depression did not benefit. The main causes of dizziness in patients without physical neuro-otologic findings were psychiatric disorders.

Keywords: SSRI, anxiety, depression, dizziness, stress

1. Introduction

In the treatment of dizzy patients, there are two major problems: first, treatment for patients without physical neuro-otologic findings, and second, therapy for patients who do have neuro-otologic deficits but do not sufficiently respond to conventional medication with
anti-vertigo drugs. Regarding the first problem, we hypothesized that dizziness in patients with a negative neuro-otologic test would be mainly due to psychiatric disorders. The second problem might be due to pro-dromal psychiatric disorders that would affect a neuro-otologic condition or to secondary psychiatric disorders following a primary neuro-otologic condition that would cause or exacerbate physical symptoms. These bidirectional relationships between neuro-otologic diseases and psychiatric disorders have previously been proposed [5,9]. For these two problems, we hypothesized that appropriate treatments for psychiatric disorders would bring about a remission of dizziness.

In this prospective study, we treated 41 consecutive dizzy patients with or without neuro-otologic diseases using fluvoxamine, one of selective serotonin reuptake inhibitors (SSRIs). We chose fluvoxamine because, to the best of our knowledge, there are no reports of the use of this drug in dizziness [3,10–12]. The outcome measures were: the Hospital Anxiety and Depression Scale (HADS), a validated 14–item self-report of anxiety and depressive symptoms [17] and subjective handicaps due to dizziness, a validated 14–item self-report of dizziness symptoms [3,7,8]. Plasma levels of vasopressin and cortisol were also measured as a hormonal stress marker [1]. All these parameters were measured before and 8 weeks after treatment. Our working hypotheses are that patients without positive neuro-otologic findings would be mainly suffering from psychiatric disorders and thus having high HADS scores and fluvoxamine would be effective on their subjective handicaps due to dizziness. We also hypothesized that fluvoxamine would be effective on subjective handicaps in neuro-otologic patients by acting on their possible comorbid psychiatric disorders. In both cases, a correlation between a recovery of subjective handicaps and HADS scores would be expected.

2. Methods

Consecutive 60 patients with complaints of dizziness who visited the Department of Otolaryngology, Osaka University Hospital, were asked whether they agreed to enter the study. Before entering the study, informed consent regarding the purpose of this study, possible effects and adverse effects of the drug was obtained from each patient. There were no patient selection criteria, however, patients whose symptoms were expected to disappear in a short time (i.e., patients with benign paroxysmal positioning vertigo or acute stage of Meniere’s disease) were excluded. This study was approved by the local ethical committee of the Osaka University Hospital and performed in accordance with the declaration of Helsinki.

2.1. Diagnosis, medical treatment and measurement of treatment outcome

Otoneurologic examinations including smooth pursuit test, observation of nystagmus with infrared CCD camera, caloric tests, posturography and pure-tone audiometry were performed. Neuroimaging such as CT or MRI/MRA of the brain and other examinations including the glycerol test and electrocochleograms were also performed if clinically indicated. Based on these examinations and careful history taking, otoneurology specialists diagnosed patients according to the guidelines for the diagnosis of vertigo and dizziness established by the Japan Society for Equilibrium Research.

During the initial one week, patients were asked to take 100 mg of fluvoxamine per os, per day. Then, during the following seven weeks, the dose was increased to 200 mg per day. Five mg of metoclopramide were also prescribed just in case nausea, an adverse effect of fluvoxamine, occurred. No other drug was used. However, if a patient was already under treatment, they were allowed to keep taking it. Anti-histamines, vasodilators, diphenidol and diuretics such as isosorbide were included in these drugs.

Subjective handicaps in daily life due to vertigo and dizziness were assessed using a dizziness and unsteadiness questionnaire as reported previously [3,7,8]. This questionnaire is a slightly modified version of the validated Jacobson’s Dizziness Handicap Inventory written in Japanese [6]. The questionnaire consisted of 14 items and as the assessment, the answers to all the questions were scored 1 to 5 on a scale in which severe handicap was scored 5, significant handicap 4, moderate handicap 3, slight handicap 2, and no handicap 1. Thus, full scores were 70 points. Table 1 shows the questions of this inventory. Questions were classified into five factors: disturbance of social activity (questions 1, 5, 9), body motion precipitating dizziness (questions 2, 6, 10), limitation of physical activity (questions 3, 7, 11), emotional disturbance (questions 4, 7, 10), and trouble with interpersonal communications (questions 1, 12, 13).

Each patient was assessed for his/her depressive or anxious status using the Japanese version of the 14-item self-report symptoms of the Hospital Anxiety and Depression Scale (HADS) [17]. While the HADS scores
Table 1
The dizziness and unsteadiness questionnaire

1. Do you refrain from going out or traveling for work or amusement due to dizziness or unsteadiness?
   (a) always
   (b) frequently
   (c) sometimes
   (d) rarely
   (e) no
   (f) no idea

2. Do you hate walking in dark places even around your home due to dizziness or unsteadiness?
   (a) absolutely
   (b) significantly
   (c) moderately
   (d) slightly
   (e) no
   (f) no idea

3. Do you hate going downstairs due to dizziness or unsteadiness?

4. Do you feel annoyed due to dizziness or unsteadiness?

5. Do you feel that you are not able to do your work either at home or at an office due to dizziness or unsteadiness?

6. Is the degree of dizziness or unsteadiness strengthened when you suddenly move your head (e.g. when looking back)?

7. Do you hate walking through narrow spaces (e.g. narrow sidewalk) due to dizziness or unsteadiness?

8. Do you feel that you are not able to do your work either at home or at an office due to dizziness or unsteadiness?

9. Are you unable to concentrate on something due to dizziness or unsteadiness?

10. Do you think it is too much trouble to read books or newspaper due to dizziness or unsteadiness? Or do you have some trouble in reading them?

11. Is the degree of dizziness or unsteadiness strengthened when you stand up from a chair?

12. Do you feel anxiety about yourself when you are in the presence of others due to dizziness or unsteadiness?

13. Do you refrain from meeting or going out with your family or friends due to dizziness or unsteadiness?

14. Do you have difficulties in your daily life due to dizziness or unsteadiness?

are not meant to offer strict diagnostic guidelines, they have been shown to be of clinical value in indicating the patient anxiety or depression status. Although most of our patients were not assessed nor diagnosed by psychiatrists, a previous study revealed that cut off point of > 12 (full scores, 42) predicted positive psychiatric disorders with 92% sensitivity while the specificity in the screening of psychiatric disorders among ENT patients was 90% [4]. Moreover, from a practical standpoint, the HADS may be more useful than psychiatric consultation to practicing otologists who must quickly judge the patients’ psychiatric status.

Before and 8 weeks after the start of fluvoxamine, we assessed HADS scores and subjective handicaps, and measured plasma levels of vasopressin and cortisol. Plasma levels of vasopressin and cortisol were measured in the morning to control the pattern of their diurnal secretion.

2.2. Patients profiles

Patients were divided into two groups: Group I comprised patients with neuro-otologic diseases diagnosed by the above mentioned vestibular tests, while Group II included those with no abnormal physical neuro-otologic findings nor vestibular diseases. Each group was made up of 30 patients. Table 2 shows the profiles of patients including age, sex, duration of dizziness, hearing levels (average for 1K, 2K, and 4K Hz of the worst hearing ear), canal paresis % (CP%), and diseases. Group I included 14 patients with Ménière’s disease, one with delayed endolymphatic hydrops, three with vestibular neuritis, and 12 with other peripheral vestibular diseases. Other peripheral vestibular diseases included 10 patients who showed unilateral caloric weakness more than 20% of CP% and 2 patients with head shake after-nystagmus. Hearing levels and CP% were significantly worse in Group I than in Group II. No differences in other parameters were found between the two groups. Note that the mean of duration of dizziness of both groups is relatively long (19.2 months for Group I and 21.2 months for Group II) indicating that most of patients had chronic dizziness.

Of the 60 patients who entered the study, 8 could not keep taking their medicine due to nausea and were thus removed from this study, and data could not be retrieved in 11 patients for an unknown reason. Therefore, data from the remaining 41 patients (Group I, n = 19; Group II, n = 22) were used to assess the effects
of fluvoxamine on various parameters. The 100 mg starting dose of fluvoxamine was relatively high and dropout by unknown reason might be a result of this dose-related nausea.

2.3. Statistical analyses

Pre-therapeutic differences in age, duration of the disease, hearing levels, caloric paresis, HADS scores and subjective handicaps between Groups I and II were tested by the Mann-Whitney U-test. Differences in subjective handicaps, HADS scores, and stress hormone levels were tested 8 weeks after treatment and compared to pre-treatment values using the Wilcoxon’s signed-ranks test. The correlation coefficient between anxious scores and depressive scores of HADS, their decline rates and subjective handicaps after 8 weeks of medication were calculated and tested using Fisher’s r to z (p-values).

3. Results

3.1. Pre-medication Hospital Anxiety and Depression Scale (HADS) and stress hormones levels

Of 30 patients with neuro-otologic diseases (Group I) and 30 of Group II with no physical neuro-otologic findings, 21 and 22 showed high pre-medication HADS scores (>12), respectively. The depressive scale in Group I and II was 7.5 ± 0.7 and 7.9 ± 0.9 (mean ± SE), respectively, while their anxious scale was 8.5 ± 0.7 and 9.4 ± 0.6 (mean ± SE), respectively. No group differences were noted between both anxious and depressive scales. As shown in Fig. 1, plasma vasopressin levels in Group I and II were 5.9 ± 1.3, and 6.5 ± 1.8 pg/mL (mean ± SE), respectively, which were higher than the normal (0.3–3.5 pg/mL). Cortisol levels in Group I and II were 15.2 ± 1.1 and 10.3 ± 0.7 µg/dL (mean ± SE), respectively, which were within normal range (4.0–18.3 µg/dL), though significantly higher in Group I than those in Group II (p = 0.0005).

3.2. Effects of fluvoxamine on subjective handicaps, HADS, and stress hormones levels

As shown in Fig. 2A, subjective handicaps were reduced following treatment in Group I (p = 0.0208). Analysis of data from patients of this group with reduced handicaps showed a significant decrease in HADS scores after treatment as compared to pre-medication values (Fig. 2B, p = 0.0131). In patients of the same group with no recovery from subjective handicaps, HADS scores were unchanged after treatment (Fig. 2C). Pre-medication HADS tended to be low in the latter subgroup compared to the former subgroup of Group I patients (11.8 ± 1.5 vs 18.1 ± 2.1, p = 0.0693). The same observations were made for patients of Group II (Fig. 3A, p = 0.0162; Fig. 3B, p = 0.0238; and Fig. 3C), though pre-treatment HADS scores of patients with no recovery from handicaps in Group II were significantly higher than those in Group I (21.5 ± 3.3 vs 11.8 ± 1.5, p = 0.0252).
In addition, analysis of data only from responders of Group I and II showed that neither vasopressin (5.2 ± 1.0 → 7.8 ± 1.7 pg/mL) nor cortisol levels (12.5 ± 1.2 → 12.4 ± 1.1 µg/dL) were decreased after the treatment.

As shown in Fig. 4A and 4B, anxious and depressive scales showed a high correlation in all patients at both pre- and post-treatment periods ($p < 0.0001$, pre: $r = 0.781$; post: $r = 0.757$). Post/pre ratio of HADS scores and subjective handicaps showed a significant correlation (Fig. 5A, $p = 0.0141$, $r = 0.388$). When only patients with decreased HADS was analyzed, subjective handicaps significantly reduced (Fig. 5B, $p < 0.0001$). In turn, HADS was significantly decreased in patients whose handicap scores were reduced (Fig. 5C, $p = 0.0015$).

HADS scores decreased from 20.7 ± 6.7 to 15.9 ± 7.6 ($p = 0.0072$) after treatment in a group of patients with high pre-treatment HADS scores (> 12).

Of 30 patients with high pre-treatment HADS scores (> 12), they decreased in 20 patients. Subjective handicaps decreased from 55.1 ± 7.0 to 42.1 ± 16.0 ($p = 0.0058$) after treatment in a group of patients with high...
pre-treatment handicap scores (> 43). Of 19 patients with high pre-treatment handicap scores (> 43), they decreased in 13 patients. It is indicated that fluvoxamine clearly had a beneficial effects on anxiety and depression and its effects on dizziness were marked in patients even with severe subjective handicaps.

4. Discussion

Staab and Ruckenstein classified otoneurologic-psychiatric interactions into three types [9]: the otogenic group, in which physical neuro-otologic conditions trigger a psychiatric dysfunction; the psychogenic group where psychiatric disorders produce dizziness; and the interactive group characterized by the exacerbation of prodromal psychiatric symptoms by neuro-otologic conditions. In any of these groups, comorbid psychiatric disorders are thought to exacerbate the dizziness of patients. The present study showed that 70% (21/30) of Group I and 73% (22/30) of Group II patients had high HADS scores (> 12), indicating that many patients with chronic dizziness had comorbid psychiatric diseases whether they had neuro-otologic diseases or not. While this percentage seemed relatively high, this was consistent with previous reports [16].

To date, no placebo controlled double blinded study has been conducted to examine the effects of SSRIs on chronic dizziness. Ideally, drug effects should be examined between a true and a negative (placebo) control drug. Because this study did not include a placebo control group, the observed effects of fluvoxamine on HADS and subjective handicaps might contain both a “true” drug effect plus “placebo” effects. Although a randomized study would be ideal, carefully designed prospective studies are also valid. For instance, as discussed below in detail, fluvoxamine showed beneficial effects only for limited patients, suggesting that this was not a placebo effect. This study is a prospective one to test the efficacy of fluvoxamine for the first time and the number of patients was larger compared to the previous studies [3,10–12]. This study would give further evidence for the use of SSRIs in the treatment of chronic dizziness.

Regarding the use of HADS without consultation to psychiatrist, a previous study revealed that cut off point of > 12 (full scores, 42) predicted positive psychiatric disorders with 92% of sensitivity while the specificity in the screening of psychiatric disorders among ENT patients was 90% [4]. Moreover, from a practical standpoint, the HADS may be more useful than psychiatric consultation to practicing otologists who must quickly judge the patients’ psychiatric status.

4.1. Group I (patients with neuro-otologic diseases)

Seventy percent of Group I patients showed high HADS scores, suggesting that many of neuro-otologic patients had comorbid pasciatric disorders that could be assigned to either the otogenic or interactive group [9]. Overall, fluvoxamine treatment was effective in Group I patients’ subjective handicaps due to dizziness (Fig. 2A). HADS scores in Group I patients whose subjective handicaps were reduced (= responders) decreased following fluvoxamine (Fig. 2B), whereas fluvoxamine had no effects on HADS scores of non-responders of Group I (Fig. 2C). Moreover, pre-treatment HADS scores of non-responders in Group I
tended to be low compared to the responders. These findings suggest that fluvoxamine was effective in controlling comorbid psychiatric disorders in neuro-otologic patients leading to a recovery from subjective handicaps in responders. If fluvoxamine contributes to recovery of vestibular function via serotonergic activation, it would be expected that the subjective handicaps should be decreased irrespective of the pre-HADS. However, fluvoxamine was only effective for patients with high pre-HADS (Fig. 2B) but not for those with low pre-HADS (Fig. 2C). These observations did not support the hypothesis that fluvoxamine might help the recovery of the vestibular function through the activation of serotonin-dependent neuronal pathways [11]. It is indicated that fluvoxamine is recommended for neuro-otologic patients with high pre-HADS (otogenic or interactive pattern) and that neuro-otologic patients with low pre-treatment HADS scores should be treated by alternative kinds of drugs acting on the vestibular system.

4.2. Group II (patients without physical neuro-otologic findings)

Overall, fluvoxamine treatment was effective in patients’ subjective handicaps due to dizziness in Group II (Fig. 3A). In responders of this group, HADS scores were also reduced (Fig. 3B), however, fluvoxamine had no effects on HADS scores in non-responders in this group (Fig. 3C). In contrast to non-responders in Group I, pre-treatment HADS scores were significantly higher than those in Group II (21.5 ± 3.3 vs 11.8 ± 1.5, p = 0.0252). Moreover, no improvement of HADS was observed even after fluvoxamine in non-responders of Group II (Fig. 3C). These findings further suggest that fluvoxamine was effective in psychiatric disorders in this group leading to a recovery from their subjective handicaps and that non-responders to fluvoxamine in Group II were suffering from more severe psychiatric disorders than very mild neuro-otologic conditions unnoticed by clinicians. Therefore, it is indicated that fluvoxamine should be used for dizzy patients without physical neuro-otologic findings and that more aggressive treatment for psychiatric disorders is recommended for non-responders in this group.

4.3. Psychiatric disorders in dizzy patients: Anxiety or depression?

Anxious and depressive scales of all patients were almost the same and it is not likely that dizzy patients are having either anxiety or depression alone (see Results). Furthermore, anxious and depressive scales showed a high correlation at both pre- and post-treatment periods (Fig. 4A, 4B). These findings suggest that dizzy patients are having both the anxiety and depression simultaneously and that fluvoxamine was effective for both the psychiatric disorders in dizzy patients. There is one more category of psychiatric disorders that could cause dizziness: undifferentiated somatoform disorders [13]. We could not rule out the possibility that some of patients with low-moderate HADS in Group II are suffering from this disorder.

4.4. Stress hormones

We measured plasma vasopressin and serum cortisol as a marker of stress. Accordingly, plasma vasopressin was higher in both Groups I and II than normal range (Fig. 1A), suggesting that the stress level of dizzy patients was higher than normal. Serum cortisol was within normal range, however, it was significantly higher in Group I than in Group II before treatment (Fig. 1B). This was consistent with a recent study that reported that serum cortisol levels were higher in Meniere’s patients as a result of disease-induced stress rather than a cause of Meniere’s disease per se [15]. Although there has been a report of complex results for cortisol levels in psychiatric disorders [14], we assume that the relatively high level of cortisol in Group I in our data may be the result of neuro-otologic diseases including Meniere’s disease. Even in patients with post-medication reduced handicaps, neither vasopressin nor cortisol decreased (see Results). This suggests that the dizziness is not the sole cause of stress in dizzy patients and that the level of stress hormones might not be a useful stress marker in dizzy patients.

4.5. Bidirectional relationship between neuro-otologic diseases and psychiatric disorders

Based on prospective observations, Jacob and Furman [5] postulated that anxiety disorders could cause psychosomatic dizziness and conversely, vestibular dysfunction could also cause somatopsychic anxiety. Moreover, Staab and Ruckenstein examined the longitudinal relationships between physical neuro-otologic illness and anxiety disorders and concluded that there is a bidirectional relationship between them [9]. This bidirectional relationship would form a “vicious cycle” and lead to chronicity of the disease. Analysis of data from all patients reveals a significant corre-
tion in the decrease of HADS scores and subjective handicaps (Fig. 5A). HADS scores were reduced following fluvoxamine treatment in the group of responders (Fig. 5B) and subjective handicaps in turn were decreased in patients whose HADS scores decreased (Fig. 5C). Since fluvoxamine was effective for comorbid psychiatric disorders in dizzy patients but not for neuro-otologic condition itself (see Group I (patients with neuro-otologic diseases) section of the Discussion), these findings indicate that psychiatric disorders have an influence on neuro-otologic conditions. Regarding the opposite direction, it has been reported that neuro-otologic conditions often trigger psychiatric disorders [2,5,9]. The present data, at least, support the concept of bidirectional relationships between neuro-otologic conditions and psychiatric disorders and suggest that fluvoxamine would be indicated to solve the “vicious cycle”.

In conclusion, dizziness in most patients without physical neuro-otological findings is due to psychiatric disorders rather than to unnoticed vestibular diseases. Overall, fluvoxamine at a dose of 200 mg per day is effective for subjective handicaps due to dizziness in patients with or without neuro-otologic illness probably by acting on both of the comorbid anxiety and depression disorders. More aggressive psychiatric treatment such as a higher dosage may be a next choice of treatment for non-responders without neuro-otologic diseases, because these patients were shown to suffer from more severe psychiatric illness (= high pre-HADS and no improvement of HADS following fluvoxamine). In contrast, other types of drugs that help recovery of the vestibular function are recommended for neuro-otologic patients without clinically significant anxiety or depression (= low pre-HADS) and non-responders to fluvoxamine.

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