Hearing Loss and Tinnitus During Fluvoxamine Treatment: A Case Report*

Duru Gündoğar[1], Fevzi Sefa Dereköy[2] , Deniz Yılmaz[3]

ÖZET:

Fluvoksamin tedavisi sırasında oluşan işitme kaybı ve tinnitus: Olgu sunumu

Fluvoksamin, yaygın olarak reçete edilen bir seçici serotonin geri alım inhibitörüdür (SSGİ). Serotoninin işitme süreçleri kapsamında önemli bir ağ oluşturduğu bilinmektedir. Son dönemde serotonin ve SSGİ'lerin işitme işlevleri üzerindeki etkisini inceleyen çalışmalar yapılmaktadır. Ancak, serotoninin işitme üzerindeki etkisi net olarak belirlenememiştir. Bu yazıda, fluvoksamin tedavisi sırasında tinnitus ve işitme kaybı gözlenen ve tedavi kesildikten sonra bu yakınmaların ortadan kalktığı bir olgu sunulmuştur. Majör depresyon tanısıyla fluvoksamin kullanmakta olan 54 yaşında kadın hastada, sağ kulakta tinnitus ve işitme kaybı şikayetleri ortaya çıktı. Hastanın tıbbi öyküsünde herhangi bir özelliğe rastlanmadı, başka herhangi bir ilaç kullanmıyordu ve kulak-burun-boğaz muayenesi tamamen normaldi. Odiometride, sağ kulakta mikst işitme kaybı gözlendi. Geçici otoakustik emisyon kayıtlarında, sağ kulakta düşük üretilebilirlik (reproducibility) ve düşük sinyal/gürültü oranı olduğu gözlendi. Fluvoksamin tedavisi kesildikten sonra yapılan kontrol incelemelerinde, işitme işlevleri normale dönmüştü. Hastamızda oluşan işitme kaybının, fluvoksamin'in fasiyal sinir işlevleri üzerindeki etkisine ve/ veya serotoninin işitsel sensorinöral iletim üzerindeki etkisine bağlı olabileceği düşünülmüştür. Olgu, klinisyenlerin SSGİ kullanımı sırasında oluşabilecek işitsel yan etkiler konusunda farkındalığını artırmak amacıyla sunulmaya değer bulunmuştur.

Anahtar sözcükler: Fluvoksamin, serotonin geri alım inhibitörleri, işitme kaybı, tinnitus

Klinik Psikofarmakoloji Bülteni 2009;19:59-63

ABSTRACT:

Hearing loss and tinnitus during fluvoxamine treatment: a case report

Fluvoxamine is a widely prescribed selective serotonin reuptake inhibitor (SSRI). Although it is known that serotonin constitutes an important network in the hearing process and there are recent studies investigating the effects of serotonin and SSRI's on the auditory functions, its exact role is not well characterized. In this paper we present a case with hearing loss and tinnitus which developed during fluvoxamine treatment and disappeared after discontinuation of fluvoxamine. A 54-year-old female patient with major depression had complaints about tinnitus and hearing loss in her right ear during fluvoxamine treatment. There were no significant abnormalities in her medical history, she was not taking any other medications, and ear-nose-throat examination was within normal limits. Audiometry revealed mixed hearing loss and transient otoacoustic emission (TOAE) recordings revealed a low reproducibility and low signal to noise ratio in the right ear. The control investigations after discontinuation of fluvoxamine revealed that the auditory functions were restored. The hearing loss in our patient might be due to the interference of fluvoxamine with facial nerve functioning or the effects of serotonin on the auditory sensorineural transmission. This case was considered to be noteworthy to publish, in order to increase clinicians' awareness of the possible side effects of SSRI's on the auditory functions.

Key words: Fluvoxamine, serotonin reuptake inhibitors, hearing loss, tinnitus

Bulletin of Clinical Psychopharmacology 2009;19:59-63

*Presented as a poster at the 39th National Psychiatry Congress, Antalya, Turkey, 14-19 October 2003.

[1]Assistant Professor of Psychiatry Suleyman Demirel University, School of Medicine Department of Psychiatry, Isparta-Turkey
[2]Associate Professor of Otolaryngology Afyon Kocatepe University, School of Medicine, Department of Otolaryngology Afyon-Turkey
[3]Associate Professor of Otolaryngology Afyon Kocatepe University, School of Medicine, Department of Otolaryngology Afyon-Turkey

Yazışma Adresi / *Address reprint requests to:* Duru Gundogar, PK:4, 32000 Isparta-Turkey

Telefon / *Phone*: +90-246-232-8902

Faks / *Fax*: +90-246-237-0240

Elektronik posta adresi / *E-mail address:* durugundogar2000@yahoo.com

Kabul tarihi / *Date of acceptance:* 10 Nisan 2007 / April 10, 2007

Bağıntı beyanı:
D.G..; F.S.D. ve D.Y.: yok.

Declaration of interest:
D.G..; F.S.D. and D.Y.: none

INTRODUCTION

Fluvoxamine, which is a member of the selective serotonin reuptake inhibitors (SSRI), is a widely prescribed antidepressant. It is true that SSRIs all have several properties in common, not the least of which is the blockade of the serotonin transporter that leads to elevation of serotonin levels throughout the central nervous system (CNS) and also throughout the entire body. Increases in serotonin levels in specific regions of the brain result in the therapeutic actions of the SSRIs. Unfortunately, the action of SSRIs on the serotonin transporter is not regionally specific, and elevation in serotonin levels in some regions of the CNS and peripheral nervous system lead to side effects (1). The most common adverse reactions to the SSRIs are gastrointestinal and neuropsychiatric, such as nausea, headache, and tremor (1,2) .

It is also known that in the central auditory pathway, serotonin can be found in many structures, from cochlear nuclei to the auditory cortex, constituting one of the most important neuromodulatory circuits in hearing processing

(3). Serotonin (5-HT) transmission forms a major modulatory network within sensory systems. This network influences various information-processing mechanisms and, in particular, filtering of auditory information (4).

Prior research has shown serotonergic pathways to interface with the auditory system, although the exact role of serotonin in the auditory system is not well characterized (5). Serotonin decreases cochlear blood flow, which could lead to cochlear microcirculation dysfunction (6). Recently there are animal and human studies investigating the effect of serotonin on the auditory neurophysiology (4,5-7) with promising results. Tadros et al (6) suggested that the upregulation of 5-HT-2B receptor gene expression with age may contribute to age related hearing loss pathogenesis.

Regarding the effects of serotonin on the hearing process, SSRIs could also be expected to cause side effects related to hearing. There are studies concerning the therapeutic effects of SSRIs in tinnitus and hearing process (8). On the contrary, it is also known that SSRIs, namely fluoxetine (9) and paroxetine (10) can cause tinnitus as a possible side effect.

A role of serotonin in persistent tinnitus was postulated by Simpson and Davies (11), based on the consideration that disrupted or modified 5-HT function might cause a reduction in auditory filtering abilities and in tinnitus habituation (12).

Up to now, there has been only one case report about subjective hearing impairment accompanied with eye tics during treatment with fluoxetine (13). To our knowledge, association of fluvoxamine with tinnitus and hearing loss has not been reported before.

The aim of this paper is to report a case in which tinnitus and objective hearing loss was observed during fluvoxamine treatment and underline the possible effects of SSRIs on the hearing process.

CASE REPORT

A 54-year-old female patient was diagnosed with major depression by the psychiatrist and she was placed on fluvoxamine (50mg/day) for two weeks. Later fluvoxamine was increased to 100 mg /day and the patient noticed a tinnitus and diminished hearing in her right ear ten weeks after the initiation of the therapy. Regarding these complaints, she was referred to the otolaryngology department. There were no significant abnormality in medical history and no history of hearing problems in the past. The patient was not on any other medication other than fluvoxamine. Ear-nose-throat examination was completely normal.

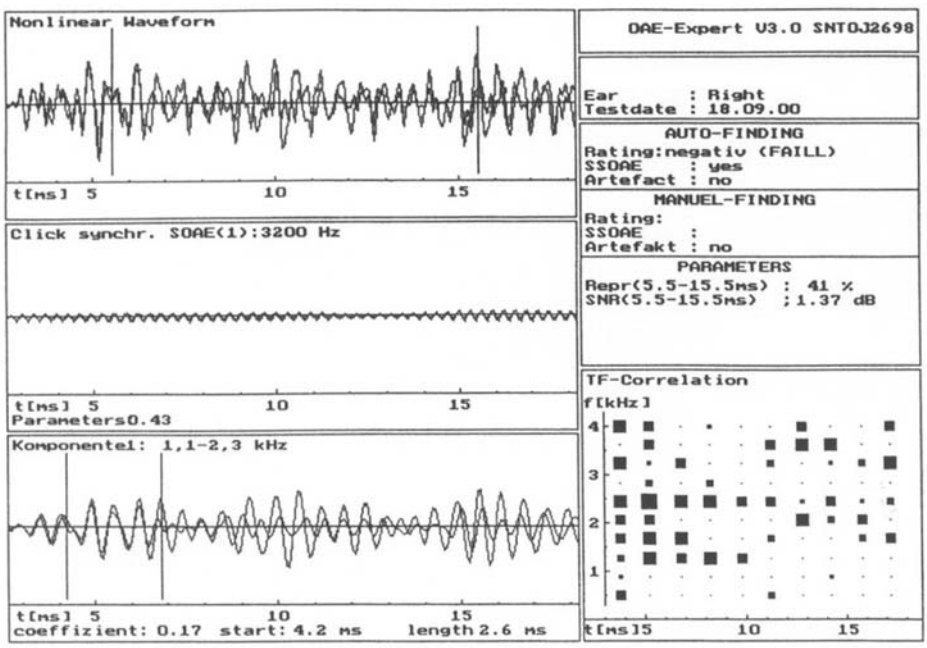

Figure 1: Transient otoacoustic emission recordings of the patient during fluvoxamine treatment

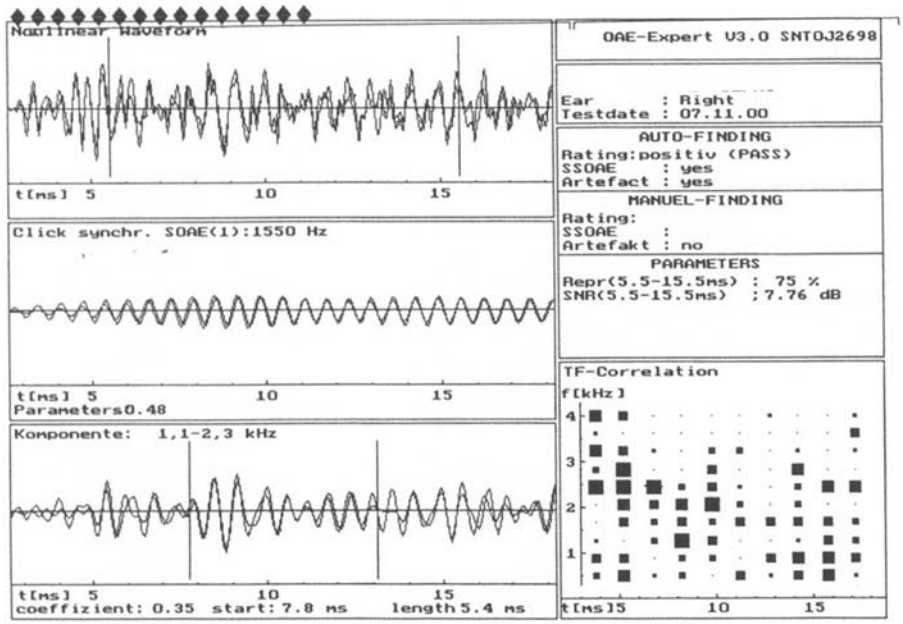

Figure 2: Transient otoacoustic emission recordings of the patient after cessation of fluvoxamine treatment

Upon further investigation, pure tone audiometry revealed a mixed hearing loss with about 35 dB threshold at 250, 500, 1000 Hz in the right ear, whereas the hearing levels at other frequencies were normal. Ipsilateral and contralateral acoustic stapedial reflex thresholds were found to be elevated (100 dB) in the pathological ear. Transient otoacoustic emission recordings (TOAE) revealed low reproducibility (40%) and low signal to noise ratio (SNR) (1.37 dB) in the right ear (Figure 1). Fluvoxamine was discontinued and the patient reported that tinnitus and hearing loss disappeared after approximately six weeks. Upon control audiometry in the 7th week following discontinuation of fluvoxamine, hearing threshold levels improved to 20 dB on the control pure tone audiometry. Ipsilateral and contralateral acoustic stapedial reflex thresholds were found to be within normal limits, that is 80 dB. Reproducibility and SNR increased to be 75% and 7,76 dB respectively (Figure 2), indicating an improvement of TOAE scores of the patient after discontinuation of fluvoxamine. Moclobemide 300 mg/day was started for the depressive symptoms and later it was increased to 450 mg/day. Follow-up interview after 4 weeks and 8 weeks revealed that the depressive symptoms started to resolve and there wasn't any hearing problem.

DISCUSSION

The unique side effects of different SSRIs have more to teach us about the mechanisms of the particular agent and the effects of serotonin on different parts of the brain (1). Although it is known that serotonin and thus SSRIs have a potential to interfere with auditory functions, to our knowledge, regarding SSRIs there has been only one case report suggesting an association between fluoxetine and hearing loss so far. In that patient, subjective hearing loss and eye tics appeared three weeks after starting fluoxetine 20 mg/day. Both eye tics and hearing loss improved to fully after approximately two weeks following the discontinuation fluoxetine but reappeared on readministration. These findings were interpreted by the authors as a possible mechanism of fluoxetine to interfere with facial nerve functioning (13).

At this point, it is interesting that Xia (7) reported fluoxetine to cause a biphasic effect on auditory cortex, increasing the spike and burst rate and burst duration at low concentrations of 1-10 μM, but beginning to decrease the network activity at 15 μM. Although it is known that the therapeutic plasma concentration of fluoxetine is 1 μM, since fluoxetine is lipid soluble with a high brain to blood ratio (7), the brain concentration can reach 20 μM

(7,14), and thus can cause an inhibitory effect on the auditory cortex.

In our patient, the hearing deficit appeared in the tenth week of treatment and thus rather later in the treatment course than the case above. However, the possibility of a subthreshold hearing deficit, which might not have been recognized by the patient until the tenth week, should also be taken into consideration. On the other hand, the hearing symptoms disappeared six weeks after the discontinuation of fluvoxamine in our patient and this time period is longer than that of Cunningham et al.'s patient, in which the time for the disappearance of the symptoms was reported to be two weeks. However it should be kept in mind that both the appearance and the resolution of the hearing deficit were subjective in Cunningham et al's case. In our case we did not prefer to readminister fluvoxamine due to possible potential of SSRIs to interfere with auditory functions.

Preclinical studies suggest that fluvoxamine has effects at σ1-receptors (15). σ receptor modulates the N-methyl-D-aspartate (NMDA)/ glutamate receptor (16,17). The σ1-receptor is abundant in the dentate gyrus of the hippocampal formation, facial nucleus, and various thalamic and hypothalamic nuclei (18).

Our patient had a mixed hearing loss in the right ear which developed during fluvoxamine treatment and resolved after discontinuation of fluvoxamine. This finding was verified by objective measurements consisting of audiometry and TOAE recordings. Since the ear-nose-throat examination was completely normal, with no history of hearing problems in the past, and the patient was not on any other medication, the symptoms are most likely to be associated with fluvoxamine use.

This effect of fluvoxamine could be caused either by interfering with the facial nerve function as suggested by Cunningham et al. (13), by affecting the facial nucleus by way of its effect on σ1 receptors, and/ or by affecting the sensorineural auditory functions related to its serotonin altering capacity.

One other possibility is that the hearing impairment was coincidental with fluvoxamine treatment in our patient. However, in our opinion, regarding the growing body of literature concerning the relationship of serotonin with auditory mechanisms, this case is noteworthy to report and should not be overlooked. Further controlled studies are warranted to clarify the effects of SSRIs in general and fluvoxamine in particular on the hearing process.

References:

1. Carrasco JL, Sandner C. Clinical effects of pharmacologic variations in selective serotonin reuptake inhibitors: an overview. Int J Clin Pract 2005; 59: 1428-1434
2. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999; 57: 507-533
3. Cruz OLM, Kase CA, Sanchez M, Barbosa F, Barros FA. Serotonin reuptake inhibitors in auditory processing disorders in elderly patients: preliminary results. Laryngoscope 2004; 114: 1656-1659
4. Liu J, Xuepei L, Wang L, Dong Y, Han H, Liu G. Effects of salicylate on serotoninergic activities in rat inferior colliculus and auditory cortex. Hear Res 2003; 175: 45-53
5. Gopal KV, Briley KA, Goodale ES, Hendea OM. Selective serotonin reuptake inhibitors treatment effects on auditory measures in depressed female subjects. Eur J Pharmacol 2005; 520: 59-69
6. Tadros SF, D'Souza M, Zettel ML, Zhu XX, Lynch-Erhardt M, Frisina RD. Serotonin 2B receptor: Upregulated with age and hearing loss in mouse auditory system. Neurobiol Aging 2006 (in press)
7. Xia Y, Gopal KV, Gross GW. Differential acute effects of fluoxetine on frontal and auditory cortex in vitro. Brain Res 2003; 973: 151-160
8. Robinson SK, Viirre ES, Stein MB. Antidepressant therapy in tinnitus. Hear Res 2006 (in press)
9. Feighner JP. A comparative trial of fluoxetine and amitriptyline in patients with a major depressive disorder. J Clin Psychiatry 1985; 46: 369-372
10. Glaxo-Smith-Kline. Product information Paxil. Philadelphia: Glaxo Smith Kline, 2002
11. Simpson JJ, Davies WE. A review of evidence in support of a role for 5-HT in the perception of tinnitus. Hear Res 2000; 145: 1-7
12. Baguley DM. Mechanisms of tinnitus. Br Med Bull 2002; 63: 195-212
13. Cunningham M, Cunningham K, Lydiard RB. Eye tics and subjective hearing impairment during fluoxetine therapy (Letter to the Editor). Am J Psychiatry 1990; 147 : 947-948
14. Karson CN, Newton JE, Livingston R, Jolly JB, Cooper TB, Sprigg J et al. Human brain fluoxetine concentrations. J Neuropsychiatry Clin Neurosci 1993; 5: 322-329
15. Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol 1996; 307: 117-119

16. Urani A, Romieu P, Portales Casamar E, Roman FJ, Maurice T. The antidepressant-like effect induced by the sigma(1) receptor agonist igmesine involves modulation of intracellular calcium mobilization. Psychopharmacology 2002; 163: 26-35

17. Bermack JE, Debonnel G. The role of sigma receptors in depression. J Pharmacol Sci 2005; 97: 317-336

18. Bouchard P, Quirion R. [3H] 1,3-di(2-tolyl)guanidine and [3H](+) pentazocine binding sites in the rat brain: autoradiographic visualization of the putative sigma1 and sigma2 receptor subtypes. Neuroscience 1997; 76: 467-477