

SSRIs and tinnitus

Introduction

Selective serotonin re-uptake inhibitors (SSRIs) are antidepressants which have been approved for the Dutch market mainly for the treatment of *depressive episodes*. The group of SSRIs consists of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and, in doses of 75-150 mg/day, venlafaxine [1].

Lareb received thirty reports of tinnitus in which an SSRI was the suspect drug. In the SPC of citalopram tinnitus is mentioned as a possible adverse drug reaction, with an incidence of 0.1% to 1% in patients using this antidepressant. The SPCs of the other SSRIs do not mention tinnitus as an adverse effect [2-7].

Tinnitus is a sensation of hearing in the absence of external sounds. It can be a benign sound that is heard only occasionally or it can be devastating roars that occur 24 hours a day accompanied by hyperacusis and the distortion of sounds. The cause of tinnitus is unknown in most cases. Tinnitus may occur together with changes in the cochlea, in the central nervous system, with intracranial hypertension, and other conditions. Tinnitus can also be drug-induced [8,9].

Reports

Up to August 24, 2005, the Netherlands Pharmacovigilance Centre Lareb received 30 reports of (severe) tinnitus in association with an SSRI. Paroxetine (13 reports), venlafaxine (9), fluvoxamine (4), citalopram (3), and sertraline (1) were associated with tinnitus. Eleven patients were male, 19 were female. Mean age was 43.5 years.

Time to onset was reported in 23 cases. In most cases tinnitus appeared within one month after start. Latency ranged from a few hours to 3.5 years after start.

In one patient tinnitus appeared one day after cessation, during withdrawal. Another patient experienced aggravation of existing tinnitus during antidepressant therapy which improved after cessation.

Of these 30 reports the outcome was reported in 26 cases. In three patients the tinnitus improved, seven patients completely recovered after cessation. One patient experienced a positive rechallenge. In five reports the patient did not recover after cessation, at the time of reporting.

Table 1. reports of tinnitus associated with the use of SSRIs

Patient, sex, age	Drug, dose	Concomitant medication	Adverse drug reaction	Time to onset, remarks, outcome
A M, 31	fluvoxamine 2 dd 50 mg	-	tinnitus	one day after start, outcome unknown
B F, 23	fluvoxamine 1 dd 100 mg	-	tinnitus, rash, tremor, chromatopsia	several hours after dose increase to 100 mg OD, outcome unknown
C M, 53	fluvoxamine 1 dd 100 mg	aspirin, omeprazole, diltiazem, clorazepate, simvastatin, clonazepam, isosorbide dinitrate	tinnitus, hearing decreased	11 days after start, positive de- and rechallenge, recovered after cessation
D F, 36	fluvoxamine 1 dd 100 mg	levothyroxine	tinnitus, vertigo	4 hours after start, recovered after cessation
E F, 55	venlafaxine 1 dd 37.5 mg	lormetazepam, promethazine,	tinnitus	12 days after start, recovered after 7

Patient, sex, age	Drug, dose	Concomitant medication	Adverse drug reaction	Time to onset, remarks, outcome
		methotrimeprazine		months on ongoing therapy
F M, 51	paroxetine 1 dd 20 mg	-	tinnitus, agitation, ejaculation disorder	19 weeks after start, recovered after cessation
G F, 32	paroxetine 1 dd 20 mg	-	tinnitus, hyperacusis, hearing loss (left ear)	27 months after start, not recovered after cessation
H M, 40	citalopram 1 dd 20 mg	lorazepam	tinnitus, hyperacusis	7 weeks after start, improved after cessation
I F, 51	paroxetine 1 dd 20 mg	-	tinnitus	8 days after start, not recovered on ongoing therapy
J F, 44	paroxetine 1 dd 20 mg	amlodipine, chlortalidone, losartan	tinnitus right ear	2 days after start, improving
K M, 76	paroxetine 1 dd 20 mg	furosemide, betaxolol, carvedilol, pilocarpine, budenoside, nifedipine, enalapril, oxiconazole, nitrate	tinnitus aggravated	aggravated after start, partly recovered after cessation
L F, 51	paroxetine 1 dd 20 mg	levothyroxine	tinnitus	3 days after start, not recovered on ongoing therapy
M M, 30	venlafaxine 2 dd 75 mg	-	tinnitus ODS	time to onset unknown, recovering after cessation
N F, 49	sertraline 1 dd 50 mg	sucralfate, paracetamol, meclizine/ pyridoxine, cotrimoxazole, bulk laxative, tramadol, ducosate/ phosphate/sorbitol, glucagon, metoclopramide, doxazosin, insulin lispro, amitriptyline, fluticasone, diclofenac, betahistine, salmeterol/- fluticasone	tinnitus, dystonia	3 days after start, recovered after cessation
O F, 40	paroxetine 1 dd 20 mg	-	tinnitus	time to onset unknown, not recovered after cessation
P F, 68	paroxetine 1 dd 20 mg	tramadol, pantoprazole, diazepam, alendronate	tinnitus ODS	time to onset unknown, not recovered on ongoing therapy
Q F, 41	citalopram dose unknown	-	tinnitus	a few days after start, not recovered after switch to fluoxetine
R M, 55	venlafaxine 1 dd 37.5 mg	-	tinnitus	2 days after start, not recovered on ongoing therapy
S F, 48	paroxetine 1 dd 20 mg	oxazepam	tinnitus	time to onset unknown, outcome unknown

Patient, sex, age	Drug, dose	Concomitant medication	Adverse drug reaction	Time to onset, remarks, outcome
T M, 61	venlafaxine 1 dd 75 mg	cimetidine, diazepam	tinnitus, hypertension	23 months after start, recovered after cessation
U F, 29	venlafaxine 1 dd 75 mg	oral contraceptive	tinnitus, restless legs	2 months after start, not recovered on ongoing therapy
V M, 31	venlafaxine 1 dd 75 mg	-	tinnitus, headache, nausea, flank pain	3.5 years after start, not recovered on ongoing therapy
W F, 23	venlafaxine 1 dd 150 mg	temazepam	tinnitus	3 months after start, recovered on ongoing therapy
X F, 53	paroxetine 1 dd 20 mg	diazepam	tinnitus, taste alteration, palpitations	time to onset unknown, outcome unknown
Y M, 44	paroxetine 1 dd 20 mg	-	tinnitus, delayed ejaculation, muscle spasm, suicide attempt, manic reaction, pruritus, abnormal vision, binge eating, fatigue	5 weeks after start, not recovered on ongoing therapy
Z F, 49	paroxetine 1 dd 20 mg	-	tinnitus	8 days after start, not recovered after cessation
AA M, 30	paroxetine 1 dd 20 mg	-	tinnitus	3 weeks after start, not recovered after cessation
AB F, 47	venlafaxine 1 dd 75 mg	bromazepam, zopiclone	tinnitus	tinnitus during withdrawal, 1 day after cessation, not recovered
AC F, 31	venlafaxine 1 dd 75 mg	-	tinnitus, balance disorder, dizziness, nausea	1 month after start, recovered after cessation
AD F, 34	citalopram 1 dd 20 mg quetiapine 1 dd 300 mg	paroxetine, temazepam, oxazepam	tinnitus aggravated	3 weeks after start, not recovered after cessation of citalopram

Other sources of information

Literature

Several publications state that most psychotropic substances, including the SSRIs, have the potential to trigger tinnitus in a small percentage of patients [9].

In a case report a patient experienced severe tinnitus three weeks after start of venlafaxine 75 mg/day. Organic causes could not be identified during EEG and MRI. Dechallenge as well as rechallenge were positive [10].

Antidepressants are sometimes used in the treatment of tinnitus. In a retrospective study on thirty patients with tinnitus and a major depression, receiving an SSRI after start of the tinnitus, effects were minimal [9].

Databases

In the Lareb database 270 reports of tinnitus are present. As mentioned, 30 of these reports concern SSRIs. Tinnitus in association with SSRIs is disproportionally present: ROR 1.97 (95% CI 1.34-2.88).

In the database of the Uppsala Monitoring Centre of the WHO tinnitus is disproportionally reported in association with citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine.

Table 2. reports of tinnitus associated with the use of SSRIs in the WHO database

	tinnitus	reports on drug	ROR (95% CI)
citalopram	81	9898	2.18 (1.75-2.71)
escitalopram	3	1058	0.75 (0.24-2.32)
fluoxetine	285	49025	1.55 (1.38-1.74)
fluvoxamine	28	6407	1.14 (0.79-1.66)
paroxetine	319	29002	2.97 (2.66-3.33)
sertraline	244	27616	2.37 (2.09-2.69)
venlafaxine	161	15350	2.81 (2.40-3.28)

Mechanism

A possible mechanism, which could explain tinnitus with vascular origin, is that serotonin has an effect on vessel tonus regulation. Sachanska examined 24 patients with tinnitus. They had serotonin blood values that significantly exceeded the reference ones. In users of SSRIs, the presynaptic serotonin reuptake is inhibited, which might result in a higher serotonin blood value [11].

Prescription data

Total number of prescriptions of SSRIs in the Netherlands is shown in table 3.

Table 3. Total number of prescriptions of SSRIs per year, 2000-2004 (Source: GIP College voor Zorgverzekeringen, Diemen)

	2000	2001	2002	2003	2004
citalopram	163920	302590	447160	567000	697740
escitalopram	-	-	-	-	1553
fluoxetine	492100	454490	439300	417830	416560
fluvoxamine	317050	284920	267400	252720	244000
paroxetine	1687800	1820200	1812400	1735900	1737900
sertraline	155700	180810	224300	258160	315560
venlafaxine	287240	380970	451090	539220	656100
Total	3103810	3423980	3641650	3770830	4069413

Conclusion

Thirty case reports of tinnitus in the Lareb database are associated with the use of SSRIs. Disproportionality in both the Lareb and the WHO database and literature support this association. The SPC of citalopram mentions tinnitus as a possible adverse effect.

References

1. Informatorium Medicamentorum. 2005 ed. KNMP; 2005.
2. Dutch SPC Cipramil[®] (version date 2003) <http://www.cbg-meb.nl/IB-teksten/19593-19594.pdf>.
3. Dutch SPC Lexapro[®] (version date 23-4-2004) <http://www.cbg-meb.nl/IB-teksten/30494-30495-30496-30497.pdf>.
4. Dutch SPC Prozac[®] (version date 29-8-2003) <http://www.cbg-meb.nl/IB-teksten/13615-15759-19429.pdf>.
5. Dutch SPC Fevarin[®] (version date 29-3-2004) <http://www.cbg-meb.nl/IB-teksten/10245-11619.pdf>.
6. Dutch SPC Seroxat[®] (version date 20-5-2005) <http://www.cbg-meb.nl/IB-teksten/14668-20557-27135.pdf>.
7. Dutch SPC Efexor[®] (version date 28-10-2004) <http://www.cbg-meb.nl/IB-teksten/16381-16382-16383.pdf>.
8. Moeller AR. Pathophysiology of tinnitus. *Otolaryngol Clin N Am* 2003;36:249-66.
9. Folmer RL, Shi Y-B. SSRI use by tinnitus patients: Interactions between depression and tinnitus severity. *Ear, Nose & Throat Journal* 2004;83(2):107-14.
10. Ahmad S. Venlafaxine and severe tinnitus. *Am Fam Physician* 1995;51(8):1830
11. Sachanska T. Changes in blood serotonin in patients with tinnitus and other vestibular disturbances. *Int Tinnitus J* 1999;5(1):24-6.