Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

SSRIs and venlafaxine in association with bruxism

Introduction

Selective serotonin re-uptake inhibitors (SSRIs) and venlafaxine 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 [1]. Venlafaxine mainly inhibits the serotonin re-uptake in doses from 75 up to 150 mg/day. In daily doses of 150 mg or more it also inhibits norepinephrine re-uptake [1]. Venlafaxine is included in this report, because three reports of bruxism were associated with this drug.

Lareb received ten reports of bruxism, or teeth-grinding in which an SSRI or venlafaxine was the suspected drug. In the SPC of venlafaxine bruxism is mentioned as a possible adverse drug reaction, with an incidence of 0.1 to 1% in patients using this antidepressant [2]. The SPCs of the SSRIs do not mention bruxism as an adverse effect [3-8].

Bruxism, is a non-specific term for numerous entities with multiple potential etiologies, most of which have a dopamine imbalance in common. “Peripheral” bruxism is caused by malocclusion, whereas “central” bruxism results from neurotransmitter perturbation [9].

Reports

Up to April 5, 2006, the Netherlands Pharmacovigilance Centre Lareb received seven reports of bruxism in association with an SSRI and three reports in association with venlafaxine.
Characteristics of the reports are shown in table 1.
In patient A the complaints were still ongoing at the time of reporting, despite cessation of paroxetine eight days prior to reporting. But she switched directly to fluoxetine. This patient also had involuntary muscle contractions and a nervous feeling which can be interpreted as extrapyramidal symptoms.
In patient B the teeth-grinding recovered after cessation, but she had permanent damage of the enamel.
Reports on patients G and H concern the same person who was using venlafaxine and switched to citalopram. She experienced nocturnal bruxism using venlafaxine 75 mg OD and tense muscles in neck, upper arms and head. Six molars were damaged. The bruxism was treated symptomatically by wearing a bit during the night and repair of the damaged molars. After cessation of venlafaxine the symptoms resolved. Six months later she received citalopram 20 mg OD and developed headache and teeth-grinding again, which recovered after cessation.

Table 1. reports of bruxism associated with the use of SSRIs and venlafaxine

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A, F, 31	paroxetine 20 mg od depression	zolpidem	teeth-grinding tremor, involuntary muscle contractions, sad and nervous feeling	six hours, not recovered after cessation
B, F, 46	citalopram 20 mg od not reported	budesonide ethinylestradiol/ norethisteron cetirizine	teeth-grinding	unknown, recovered with sequel (permanent damage of enamel) after cessation
C, F, 36	paroxetine 20 mg od depression	not reported	teeth-grinding	one week, unknown
D, M, 32	fluoxetine 20 mg od not reported	esomeprazole hydrochloro-thiazide amlodipine	teeth-grinding	unknown, unknown
E, F, 36	paroxetine 20 mg od depression	none	teeth-grinding apathy face oedema	two weeks, recovered after cessation
F, F, 45	fluvoxamine 100 mg od depression	not reported	teeth-grinding flatulence	eight weeks, unknown
G, F, 63	citalopram 20 mg od depression	oxazepam	teeth-grinding headache	unknown, recovered after cessation
H, F, 63	venlafaxine 75 mg od depression	risperidone 1 mg od	diurnal and nocturnal teeth-grinding tense muscles in neck, head and upper arms	unknown, teeth-grinding was treated with a bit during the night
I , F, ?	venlafaxine 75 mg od	OAC containing ethinylestardiol and norgestrel	teeth-grinding pruritus	weeks, unknown
J , M, 58	venlafaxine 75 mg od	hydrochlorothiazide/ losartan atorvastatine vitamins	teeth-grinding early morning awakening constipation decreased libido erectile dysfunction	days, recovering on ongoing therapy

Other sources of information

Literature

Several case reports describe twenty patients experiencing (nocturnal) bruxism during treatment with SSRIs [9-14]. Three typical cases are described here.
One patient experienced nocturnal teeth-grinding ten days after a dose increase of citalopram 20 mg/day to 40 mg/day. The bruxism developed to such an extent that extraction of a molar was required [10].
A 20-year-old woman with no history of dental damage was prescribed 10 mg paroxetine OD. After dose increase to 20 mg OD she experienced tooth pain, jaw tenderness and teeth-grinding. The dentist noted that the patient's teeth appeared

damaged in what he believed to be a pattern consistent with the grinding and clenching of teeth [13].
A 50-year old man was prescribed venlafaxine 37.5 mg BID. After one week the dose was increased to 75 mg BID. Five weeks after initiation the patient reported anxiety, tremor, insomnia and teeth-clenching and -grinding during day and night. He described awakening with sore jaws and teeth [12].

Databases

On 5 april 2006 the Lareb database contains seven reports of bruxism in association with SSRIs, three in association with venlafaxine. In total the database contains eleven reports of bruxism. Bruxism in association with SSRIs is disproportionally present: ROR 34.0 (95% CI 9.9-116). Bruxism in association with venlafaxine is also disproportionally present: ROR 32.1 (95% CI 8.5-121).

In the database of the Uppsala Monitoring Centre of the WHO bruxism is disproportionally reported in association with citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine (table 2).

Table 2. reports of bruxism associated with the use of SSRIs and venlafaxine in the WHO database

	bruxism [n]	reports on drug [n]	ROR (95% CI)
citalopram	19	9898	16.7 (10.5-26.5)
escitalopram	3	1058	23.7 (7.6-74.1)
fluoxetine	31	49025	5.6 (3.8-8.1)
fluvoxamine	7	6407	11.7 (5.5-24.8)
paroxetine	64	29002	21.7 (16.6-28.3)
sertraline	64	27616	22.8 (17.4-29.8)
venlafaxine	35	15350	20.7 (14.6-29.3)

Mechanism

Serotonergic neurons project from the Raphe nucleus to the ventral tegmental area (VTA) of the midbrain, where they synapse with the cell bodies of dopaminergic neurons that project to the prefrontal cortex via the mesocortical tract. The dopamine neurons in the VTA contain 5-HT_2 heteroceptors at the cell body and at the synapse. When occupied by serotonin, the 5-HT_2 heteroceptors at the dopamine cell body decrease the firing of the neuron, while, at the same time, those at the synapse serve to down-regulate synaptic dopamine release.
The result is that dopamine decreases in the mesocortical tract. Within this tract, dopamine inhibits spontaneous movement. A decrease in dopamine increases disinhibition, with characteristic repetitive muscle contractions of bruxism [9].

Prescription data
Total number of prescriptions of SSRIs and venlafaxine in the Netherlands is shown in table 3.

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

	2000	2001	2002	2003	2004
citalopram	163,920	302,590	447,160	567,000	697,740
escitalopram	-	-	-	-	1,553
fluoxetine	492,100	454,490	439,300	417,830	416,560
fluvoxamine	317,050	284,920	267,400	252,720	244,000
paroxetine	1,687,800	1,820,200	1,812,400	1,735,900	1,737,900
sertraline	155,700	180,810	224,300	258,160	315,560
venlafaxine	287,240	380,970	451,090	539,220	656,100
total	**3,103,810**	**3,423,980**	**3,641,650**	**3,770,830**	**4,069,413**

Conclusion

Ten reports of bruxism in the Lareb database are associated with SSRIs and venlafaxine. Disproportionality in both the Lareb and the WHO database and a possible mechanism support this association.

References

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