Paroxetine and bruxism – an update

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 and sertraline [1].

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 [2]. It can cause serious and irreversible tooth damage.

In the SmPC of sertraline, citalopram, escitalopram and fluoxetine bruxism is mentioned as a possible adverse drug reaction [3-6]. The SmPC from paroxetine does not mention bruxism. Extrapyramidal disorders including orofacial dystonia, of which bruxism can be a part, are mentioned, but does not specify bruxism [7].

In Quarterly Report 2007-1, the Netherlands Pharmacovigilance Centre Lareb described bruxism associated with SSRI’s and venlafaxine [8]. Since bruxism is now labelled in the SmPC of most other SSRIs, apart from paroxetine, this report gives an update of reports and literature about the association between bruxism and this drug,

Reports

From December 1986 until June 2017, the Netherlands Pharmacovigilance Centre Lareb received 12 reports of bruxism with the use of paroxetine [9]. The details of these reports are presented in table 1.

7 Reports concerned female and 5 reports male patients. The age varied from 19 until 50 years, the mean age was 35 years. The time to onset for bruxism varied from 6 hours to 13 years, with a median of 4 days. 4 Reports showed a positive dechallenge (A, D,E, K). In report E a positive rechallenge was performed. In one case, at time of reporting, the patient was not recovered after withdrawal (C), and in another case the patient was not recovered after dose reduction (F). In 5 reports (B,G,H,J,L), the dose for paroxetine was not changed, and 3 of these patients were not recovered at time of reporting (G,H,L). The patient in report J was recovering without changes in the dose of paroxetine. In report B the outcome for bruxism was unknown. The patient in report G also used methylphenidate, for which bruxism is a known adverse event.

Table 1. Reports of bruxism during the use of paroxetine [9].

Number, Sex, Age, Reporter	Suspect drug, Dose, Indication	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
A. 22680 F, 31-40 years, General Practitioner	Paroxetine tablet 20mg 1dd1t, Depressive episode		Bruxism Apathy Face oedema	2 Weeks, Drug withdrawn, Recovered
B. 50795 F, 31-40 years, General Practitioner	Paroxetine tablet 20mg 1dd1t, Depression		Bruxism	1 Week, Dose not changed, Unknown
C. 52742 F, 31-40 years, Consumer	Paroxetine tablet 20mg 1dd1t, Depression	Zolpidem	Bruxism, Tremor, Dyspnoea, Muscle contractions involuntary, Emotional disorder	6 Hours, Drug withdrawn, Not recovered

Number, Sex, Age, Reporter	Suspect drug, Dose, Indication	Concomitant medication	Reaction	Time to onset, Action with drug, Outcome
D. 64320 M, 31-40 years, General Practitioner	Paroxetine tablet 20mg 1dd1t, Insomnia		Bruxism	4 Days, Drug withdrawn, Recovered
E. 86167 F, 41-50 year Physician	Paroxetine tablet 20 mg 1d 0,5 t Depressed mood		Bruxism	13 years, Drug withdrawn Recovered
F. 86768 M, 41-50 years, General Practitioner	Paroxetine tablet 20mg 1dd1t, Agitation	Omeprazole Diclofenac Valsartan Acetylsalicylic acid	Bruxism	2 Days, Dose reduced, Not recovered
G. 115510 F, 21-30 years, Consumer	Paroxetine tablet 20mg 1dd1t Depression Methylphenidate tablet mga 36mg, 1dd1t, Attention deficit-hyperactivity disorder	Fluticasone	Bruxism, Skin hyperpigmentation, Dry mouth, Restless legs syndrome	PAROXETINE TABLET FO 20MG 9 Years, Dose not changed, Not recovered
H. 150573 F, 11-20 years Consumer	Paroxetine tablet 10mg 1dd1t, Depression		Bruxism	3 Weeks, Dose not changed, Not recovered
I. 169956 M, 41-50 years Consumer	Paroxetine tablet 20mg 1dd1t, Depression	Budesonide Omeprazole	Bruxism	3 Months, Not applicable, Not recovered
J. 216941 F, 11-20 years, Consumer	Paroxetine tablet 20mg 1dd1t, Panic disorder		Bruxism	2 Days, Dose not changed, Recovering
K. 227387 M, 41-50 years, General Practitioner	Paroxetine tablet 10mg 1dd1t, Depression		Bruxism	2 Days, Drug withdrawn, Recovered
L. 234537 M, 31-40 years, Consumer	Paroxetine tablet 20mg, 1dd1t, Depression		Bruxism, Paraesthesia, Vision blurred	Unknown Days, Dose not changed, Not recovered

Other sources of information

SMPC's

The Dutch SmPCs of paroxetine do not mention bruxism as an adverse drug reaction [7]. The SmPCs of other SSRI's do mention bruxism as an adverse drug reaction [3-6]. The FDA label of paroxetine mentions bruxism as an infrequent adverse event [10].

Literature

The association has been described in the literature for paroxetine as well as for other SSRIs [2,11-16]. A case-report is described in more detail below:

Possible paroxetine-induced bruxism (ie, grinding and clenching of the teeth, usually during sleep) followed treatment with paroxetine 10 milligrams (mg) daily in the morning for 5 days, increasing to 20 mg daily. Four months later, routine dental cleaning revealed damaged teeth consistent with bruxism. Tooth damage or temporomandibular joint dysfunction were not observed at previous dental visits. The 20-year-old woman's only other medication was tetracycline 250 mg twice daily for acne. On the fourth day after addition of oral buspirone 5 mg at bedtime the patient reported a significant reduction

of gritting, tooth pain, and jaw tenderness [15].
Lareb published several articles about the association between SSRIs and bruxism [17-19].

Databases

Table 2. Reports of the PT “Bruxism” associated with paroxetine, in the Lareb [9], WHO [20] and Eudravigilance database [21].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Bruxism	12	18.1 (9.7-33.7)
WHO	Bruxism	139	11.6 (9.8-13.8)
Eudravigilance	Bruxism	43	9.2 (6.8-12.5)

Prescription data

Table 3. Number of patients using paroxetine in the Netherlands between 2011 and 2015 [22].

Drug	2011	2012	2013	2014	2015
Paroxetine	196,670	191,190	184,860	179,840	174,080

Mechanism

SSRIs are known to cause extrapyrimidal symptoms [1]. 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 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 [2].

Discussion and conclusion

For almost all SSRIs on the Dutch market, except fluvoxamine and paroxetine, bruxism is labelled in the SmPC. Lareb received a total of 12 reports of bruxism associated with the use of paroxetine, including four with a positive dechallenge and one with a positive rechallenge. Lareb also received 16 cases of bruxism for other SSRIs, namely citalopram (n=7), fluoxetine (n=4), escitalopram (n=2), fluvoxamine (n=2), sertraline (n=1) [9]. Based on the reported cases, literature [2,11-16] and the mechanisms proposed in the literature, a class-effect seems likely.
Bruxism can be part of extrapyramidal symptoms, which are mentioned in the SmPC of paroxetine [7]. Healthcare professionals probably recognize bruxism as a symptom of an extrapyramidal adverse drug reaction. However, for patients this is probably not evident. Since bruxism can cause serious and irreversible tooth damage, patients should be aware that this adverse drug reaction may occur.

References

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This signal has been raised on September 11, 2017. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl